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# Journal of PSYCHOPATHOLOGY

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# Features and pharmacotherapy of treatment-resistant depression: an observational study on hospitalized patients

Gabriele Di Salvo<sup>1</sup>, Francesco Cuniberti<sup>1</sup>, Matteo Bianco<sup>1</sup>,  
Donatella Ramello<sup>2</sup>, Giuseppe Maina<sup>1,2</sup>, Gianluca Rosso<sup>1,2</sup>

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## SUMMARY

### Objectives

Treatment-resistant depression (TRD) is a complex and debilitating condition with heavily impacting consequences on healthcare and socio-economic system. The overall picture of TRD still appears conflicting and fragmentary and most studies were conducted on outpatients only.

Aim of this study was to investigate the characteristics of real-world inpatients with TRD in order to provide useful information in daily clinical practice and identify any specific feature of this population.

### Methods

We retrospectively examined clinical charts of 250 MDD inpatients, excluding subjects with any type of bipolar disorder. Patients were grouped in two sub-samples, TRD and non-TRD (nTRD); socio-demographic and clinical characteristics were compared between the two sub-groups. Furthermore, therapeutic strategies adopted in TRD patients were analysed. Comparisons were performed by using Pearson's  $\chi^2$  test with Yates' correction for categorical variables and independent-samples t-test for continuous variables.

### Results

The prevalence of TRD in our sample was 32.4%. Compared to nTRD subjects, TRD inpatients were significantly older, while unexpectedly other socio-demographic factors, such as lower educational level and unemployment, did not result associated to TRD. Concerning clinical features, TRD subjects had longer duration of illness, more lifetime depressive episodes, older age at first admission and higher rate of family history for mood disorders and for suicide. They also showed greater severity of the current episode, less comorbid psychiatric disorders and more medical conditions. The lack of correlation between suicidality and TRD was an unexpected result. At discharge, TRD was more related to polypharmacy with higher number of psychotropic drugs in particular; add-on was the most frequent strategy (48.1%) and the atypical antipsychotics (quetiapine above all) were the most frequent add-on medications (68.8%).

### Conclusions

We observed several peculiar features of TRD in hospitalized patients that have not been described previously. Further research is awaited to investigate such relationships and help detecting valid therapeutic strategies in inpatients.

**Key words:** major depressive disorder, treatment-resistant depression, inpatients, suicide, treatment strategies

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### Conflict of interest

The Authors declare no conflict of interest

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## Introduction

Over recent years, Major depressive disorder (MDD) has held great importance in public health due to its increase in both prevalence and consequent disability rate<sup>1</sup>. According to the World Health Organization, it is estimated that by 2030 MDD will have become the leading cause of disability worldwide<sup>2</sup>.

Despite such considerable impact of depression, there is still lack of consistently effective medication, as only a few amount of patients manage to achieve full remission with currently available pharmacological treatments<sup>3,4</sup>. Among those who show initial response, up to 50% maintain residual symptoms with high risk of relapse and progression to chronicity<sup>5,6</sup>. Moreover, around 30-40% of patients show no response to first-line treatments and more than 50% do not improve after prescription of a second different antidepressant (AD)<sup>7</sup>, thus presenting signs of a resistant disease.

Lack of consensus exists about the concept of treatment-resistant depression (TRD)<sup>8</sup>. A widely used practical criterion for TRD is a minimum of two prior treatment failures and confirmation of prior adequate dose and duration of treatment<sup>9</sup>.

However, TRD is a complex and debilitating condition with heavily impacting consequences on healthcare and socio-economic system<sup>10</sup>. Crown and colleagues found that TRD patients present twice the probability of hospital admission, with overall average costs up to six times higher compared to patients with non-TRD<sup>11</sup>.

In the recent past a vast literature has deepened socio-demographic and clinical factors related to TRD. The impact of age in failure to respond to AD medication has been broadly investigated, with mixed results<sup>12</sup>: although the majority of studies did not show significant correlation between age and unresponsiveness to treatment, a few found that older age might be associated with lower response to ADs<sup>13</sup>; gender did not seem to be related to responsiveness to treatment<sup>14,15</sup> nor with remission rate<sup>16</sup>. Other variables such as occupation, poor level of education and being divorced or widower were detected as possible predictive factors of TRD<sup>15,17-20</sup>.

Concerning clinical variables, age at onset<sup>19,21</sup>, severity of depressive symptoms<sup>15,19,22</sup>, psychotic and anxiety features<sup>19</sup>, number of lifetime depressive episodes<sup>14</sup> and family history for psychiatric disorders including bipolar disorder and suicide<sup>17,18,19</sup> did not appear significantly associated with lack of response to antidepressants. Conversely, melancholic symptoms showed a significant association with lower response<sup>18</sup> as well as length of major depressive episode (MDE)<sup>16,19</sup> and lifetime hospitalization rate<sup>17,18</sup>. Suicide attempt (current) and history of multiple suicide attempts suggested lower response rate to therapies<sup>13,18</sup>; furthermore, existing studies indicated that TRD presents a three-fold higher lifetime suicide attempt rate (17% in TRD vs 6% in nTRD)<sup>22</sup>. Lastly, evidence concerning the role of comorbid disorders showed mixed results: anxiety and substance use disorders seemed to be associated with higher treatment resistance in most studies<sup>16,18</sup>, while relationship between TRD and personality disorders

was controversial<sup>23,24</sup>; medical conditions were identified as a risk factor for TRD<sup>25</sup> with special reference to thyroid diseases and subclinical hypothyroidism in particular<sup>26</sup>.

In light of these findings, the overall picture of TRD still appears conflicting and fragmentary. Furthermore, although TRD patients present twice the probability of hospital admission, with overall average costs up to six times higher compared to patients with non-TRD<sup>11</sup>, most studies were conducted on outpatients only<sup>9</sup>.

Therefore, aim of this study was to investigate the characteristics of real-world inpatients with TRD in order to provide useful information in daily clinical practice and identify any specific feature of this population.

## Materials and methods

### Study design and patients

This is an independent observational study with retrospective design.

Clinical charts of 250 patients admitted to the Psychiatric Inpatient Unit of San Luigi Gonzaga Hospital of Orbassano (Turin, Italy) with principal diagnosis of MDD (DSM-5) from January 2016 to December 2018 were reviewed by residents in psychiatry supervised by senior psychiatrists with several years of clinical experience in diagnosis and treatment of depression. Particular attention was paid to the exclusion of all patients with any subtype of bipolar disorder, including bipolar disorder NOS or patients with soft bipolar spectrum.

The present analysis is part of an independent observational study on clinical features of mood disorders which has been reviewed and approved by the local Ethical Committee.

### Assessment and procedures

Patients were grouped in two sub-samples, TRD and non-TRD (nTRD), according to whether or not they presented a TRD according to the operational definition, which requires a minimum of two prior treatment failures and confirmation of prior adequate dose and duration<sup>9</sup>. Any case of pseudo-resistance that emerged through detailed examination of clinical charts (e.g. patients who have responded by simply increasing the dosage of the antidepressant compound at admission) was included in nTRD subgroup.

Clinical features examined in our study included:

- psychiatric history of MDD: age at onset, number of lifetime episodes, duration of illness;
- psychiatric family history (with particular regard to mood disorders);
- current episode features: symptoms and severity;
- hospitalization details: length, type of discharge;
- suicidality: current and lifetime suicide attempt rate;

- psychiatric and medical comorbidities;
- AD treatment during the current major depressive episode (MDE) before hospital admission;
- psychiatric and non-psychiatric treatment at discharge.

Furthermore, therapeutic strategies adopted in TRD patients during the hospital stay were analysed, grouping them as follows: (a) switch to other AD belonging to either the same or different pharmaceutical category; (b) combination with a second AD; (c) add-on of a drug not classified as antidepressant to current AD medication (augmentation strategy)<sup>27,28</sup>.

Optimization strategy was not considered since patients who were prescribed low AD doses before admission and who showed response to dose increase of the same AD during hospitalization were included in the non-TRD group.

### Statistical analysis

Socio-demographic and clinical features of the patients were summarized as mean and standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables.

Comparison between socio-demographic and clinical features of the two groups was performed by using Pearson's  $\chi^2$  test with Yates' correction for categorical variables and independent-samples t-test for continuous variables.

All statistical analyses were performed by SPSS software version 26.0.

### Results

Two-hundred and fifty clinical charts of inpatients admitted with principal diagnosis of MDD (according to the DSM-5 criteria) were analysed. One-hundred twenty-six patients (50.4%) were female, 124 (49.6%) were male. Eighty-one patients (32.4%) fulfilled the criteria for TRD. Socio-demographic and clinical characteristics of the total sample and differences between TRD and nTRD subjects are given in Table I.

TRD patients were significantly older than nTRD patients (years, TRD  $55.3 \pm 14.8$  vs nTRD  $48.5 \pm 16.3$ ,  $p = 0.002$ ). There were no significant differences noticed either in gender or in educational, marital and occupational status.

Regarding clinical features, the following results were found:

- psychiatric history: subjects diagnosed with TRD had longer duration of illness (TRD  $19.6 \pm 15.8$  vs nTRD  $11.9 \pm 14.0$ :  $p < 0.001$ ), more lifetime depressive episodes (TRD  $3.2 \pm 1.6$  vs nTRD  $2.6 \pm 1.6$ :  $p = 0.003$ ) and older age at first admission (years, TRD  $44.6 \pm 14.7$  vs nTRD  $41.8 \pm 17.4$ :  $p = 0.027$ );
- psychiatric family history: TRD patients had higher

rate of positive psychiatric family history in I and II grade relatives (TRD 54.3% vs nTRD 40.8%:  $p = 0.045$ ), in particular for suicide (TRD 14.8% vs nTRD 4.1%:  $p = 0.003$ ) and mood disorders (TRD 50.6% vs nTRD 28.4%:  $p = 0.001$ ), although no significant difference was found for bipolar disorder (TRD 0.0% vs nTRD 3.0%:  $p = 0.118$ );

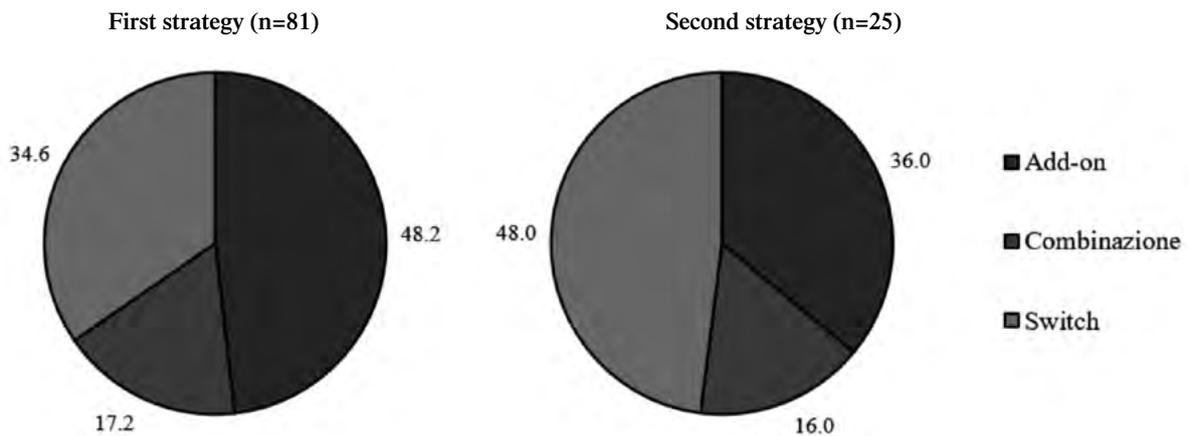
- current episode features: subjects with TRD showed higher rate of melancholic features (TRD 12.3% vs nTRD 3.6%,  $p = 0.008$ ) and greater severity of the current episode (TRD 42.0% vs nTRD 28.4%:  $p = 0.032$ );
- hospitalization details: no difference was found in length of hospitalization (days, TRD  $8.9 \pm 4.8$  vs nTRD  $7.8 \pm 6.0$ :  $p = 0.161$ ) and type of discharge (e.g. discharge at home, TRD 69.1% vs nTRD 75.7%:  $p = 0.268$ );
- suicidality: neither current (TRD 16.0% vs nTRD 21.0%:  $p = 0.328$ ) nor lifetime (TRD 25.9% vs nTRD 27.8%:  $p = 0.754$ ) suicide attempt rate was found to be significantly higher in TRD patients;
- psychiatric comorbidities: patients with TRD showed lower rate of psychiatric comorbidities (TRD 39.5% vs nTRD 53.8%:  $p = 0.034$ ). Notwithstanding, no statistically significant correlation was noticed between TRD and specific comorbid disorders, such as alcohol/drug use disorder (TRD 14.8% vs nTRD 20.1%:  $p = 0.311$ ), personality disorders (TRD 22.2% vs nTRD 16.6%:  $p = 0.280$ ), anxiety disorders (TRD 2.5% vs nTRD 7.1%:  $p = 0.136$ ) and obsessive-compulsive disorder (TRD 6.2% vs nTRD 8.9%:  $p = 0.461$ );
- medical comorbidities: TRD patients had higher rate of medical comorbidities (TRD 73.3% vs nTRD 54.4%:  $p = 0.002$ ), in particular hypothyroidism (TRD 23.5 vs nTRD 11.8%:  $p = 0.018$ );

AD treatments before admission: as first trial, SSRI were the most prescribed (79.0%), citalopram above all (29.6%); as second and third trial, SNRI were as prescribed as SSRIs (second trial: both 32.1%; third trial: SNRI 30.8% vs SSRI 34.6%) and venlafaxine was the most used drug (18.5% and 19.2% at second and third trial respectively);

treatments at discharge: TRD patients were prescribed more AD drugs (TRD  $1.3 \pm 0.6$  vs nTRD  $1.0 \pm 0.5$ :  $p = 0.003$ ) and in particular SNRIs (TRD 32.1% vs nTRD 17.2%:  $p = 0.008$ ), but less SSRIs (TRD 45.7% vs nTRD 60.4%:  $p = 0.003$ ). Moreover, subjects with TRD were given more antipsychotics (TRD 51.9% vs nTRD 34.3%:  $p = 0.002$ ) and lithium (TRD 19.8% vs nTRD 3.0%:  $p < 0.001$ ), but less benzodiazepines (TRD 27.2% vs nTRD 44.4% vs:  $p = 0.009$ ). It is noteworthy that subjects with TRD were prescribed a higher number of both psychiatric (TRD  $2.4 \pm 0.8$  vs nTRD  $2.1 \pm 0.8$ :  $p = 0.014$ ) and overall (TRD  $3.9 \pm 1.7$  vs nTRD  $3.2 \pm 1.7$ :  $p = 0.008$ ) medication compared with nTRD patients.

**TABLE I.** Socio-demographic and clinical characteristics of the total sample ( $n = 250$ ) and differences between TRD ( $n = 81$ ) and nTRD ( $n = 169$ ) patients.

Characteristics	Total sample ( $n = 250$ )	TRD ( $n = 81$ )	nTRD ( $n = 169$ )	t/ $\chi^2$	P
Age (years), mean $\pm$ SD	50.7 $\pm$ 16.1	55.3 $\pm$ 14.8	48.5 $\pm$ 16.3	-3.147	<b>0.002</b>
Gender, n (%)				1.957	0.162
– Female	126 (50.4)	46 (56.8)	80 (42.3)		
– Male	124 (49.6)	35 (43.2)	89 (57.7)		
Marital status, n (%)				5.840	0.119
– Single	89 (35.6)	24 (29.6)	65 (38.5)		
– Married/coupled	116 (46.4)	39 (48.1)	77 (45.6)		
– Divorced	28 (11.2)	14 (17.3)	14 (8.3)		
– Widower	17 (6.8)	4 (4.9)	13 (7.7)		
Education (years), mean $\pm$ SD	8.6 $\pm$ 3.3	8.7 $\pm$ 3.1	8.5 $\pm$ 3.4	0.665	0.673
Occupation, n (%)				3.556	0.469
– Working for pay	100 (40.0)	33 (40.7)	67 (39.6)		
– Housewife	21 (8.4)	7 (8.6)	14 (8.3)		
– Retired	23 (9.2)	8 (10.0)	15 (8.9)		
– Student	21 (8.4)	3 (3.7)	18 (10.7)		
– Unemployed	85 (34.0)	30 (37.0)	55 (32.5)		
Age at onset (years), mean $\pm$ SD	36.5 $\pm$ 16.8	35.7 $\pm$ 15.5	36.4 $\pm$ 17.3	0.506	0.613
Duration of illness (years), mean $\pm$ SD	14.4 $\pm$ 15.0	19.6 $\pm$ 15.8	11.9 $\pm$ 14.0	-3.898	<b>&lt; 0.001</b>
Depressive episodes (number), mean $\pm$ SD	2.8 $\pm$ 1.6	3.2 $\pm$ 1.6	2.6 $\pm$ 1.6	-2.981	<b>0.003</b>
Hospitalizations (number), mean $\pm$ SD	2.0 $\pm$ 1.4	2.2 $\pm$ 1.2	1.9 $\pm$ 1.4	-1.088	0.123
Age at first admission (years), mean $\pm$ SD	42.6 $\pm$ 17.4	44.6 $\pm$ 14.7	41.8 $\pm$ 17.4	-6.743	<b>0.027</b>
Psychiatric family history in 1st and 2 <sup>nd</sup> degree relatives, n (%)	113 (45.2)	44 (54.3)	69 (40.8)	4.024	<b>0.045</b>
Psychiatric family history for specific diseases, n (%)					
– Mood disorders	89 (35.6)	41 (50.6)	48 (28.4)	11.787	<b>0.001</b>
– Bipolar disorders	5 (2.0)	0 (0.0)	5 (3.0)	2.445	0.118
– OCD	19 (7.6)	1 (1.2)	8 (4.8)	1.952	0.162
– Suicide	19 (7.6)	12 (14.8)	7 (4.1)	18.882	<b>0.003</b>
Current episode features, n (%)					
– Psychotic	19 (7.6)	7 (8.6)	12 (7.1)	0.185	0.667
– Melancholic	16 (6.4)	10 (12.3)	6 (3.6)	7.071	<b>0.008</b>
– Anxiety	54 (19.6)	15 (18.5)	39 (23.1)	0.672	0.412
Current episode severity, n (%)				4.577	<b>0.032</b>
– Moderate	168 (67.2)	47 (58.0)	121 (71.6)		
– Severe	82 (32.8)	34 (42.0)	48 (28.4)		
Length of hospitalization (days), mean $\pm$ SD	8.1 $\pm$ 5.7	8.9 $\pm$ 4.8	7.8 $\pm$ 6.0	-1.395	0.161
Type of discharge, n (%)				1.229	0.268
– Home	184 (73.6)	56 (69.1)	128 (75.7)		
– Nursing home	66 (26.4)	25 (30.9)	41 (24.3)		
Suicide attempt leading to current hospitalization, n (%)	49 (19.6)	13 (16.0)	36 (21.0)	0.995	0.328
Current suicide attempt features, n (%)				3.453	0.632
– Nonviolent	41 (83.7)	13 (100)	28 (77.8)		
– Violent	8 (16.3)	0 (0.0)	8 (22.2)		
Lifetime suicide attempts, n (%)	68 (27.2)	21 (25.9)	47 (27.8)	0.098	0.754
Psychiatric comorbidities, n (%)	123 (49.2)	32 (39.5)	91 (53.8)	4.505	<b>0.034</b>
Specific psychiatric comorbidities, n (%)					
– Alcohol/substance use disorder	46 (18.4)	12 (14.8)	34 (20.1)	1.026	0.311
– Personality disorder	46 (18.4)	18 (22.2)	28 (16.6)	1.116	0.280
– Anxiety disorder	14 (5.6)	2 (2.5)	12 (7.1)	2.222	0.136
– Obsessive-compulsive disorder	20 (8.0)	5 (6.2)	15 (8.9)	0.544	0.461
Medical comorbidities, n (%)	153 (61.2)	61 (73.3)	92 (54.4)	10.044	<b>0.002</b>



**FIGURE 1.** *treatment strategies employed in TRD patients (n = 81) in our sample.*

Depending on the individual clinical response, a therapeutic strategy or a combination of two of the three strategies were adopted. A single strategy was preferred in most cases (69.1%), and add-on therapy was the most frequent choice (48.1%). Antipsychotics resulted in being the most frequently chosen add-on medication (68.8%), among which quetiapine (63.6%) and aripiprazole (27.3%) were the most prescribed drugs; lithium was the second most used treatment as an add-on strategy (25.0% of total). Switch to another AD was also a frequently used option (34.6%), while combination was the least preferred strategy (17.2%).

Data regarding treatment strategies employed in TRD patients is shown in Figure 1.

## Discussion and conclusions

Although TRD is commonly diagnosed and treated in psychiatric wards, the population of TRD inpatients has been scarcely investigated. The purpose of the study was to deepen the knowledge of TRD features in real-world inpatients in order to provide useful information for clinicians operating in acute care hospital facilities and identify any specific characteristics of TRD in this population.

The total sample of inpatients with MDD (TRD and n-TRD) was composed in almost equal parts by females (50.4%) and males (49.6%). This is a rather unexpected finding, since MDD is widely known to be twice as frequent in females as in males<sup>29</sup>; moreover, inpatient settings usually include subjects with severe disease features, who are mostly women according to the literature on depressive disorders<sup>30</sup>. Regarding main psychiatric history features (such as age at onset and clinical course), the MDD sample conforms to recent findings in literature<sup>31,32</sup>.

The rate of TRD (32.4%) is consistent with values reported in previous papers<sup>33</sup>. TRD patients presented older age compared to non-TRD, while being unemployed, lower educational level as well as being divorced/widower were not associated to treatment resistance in our sample, in contrast with findings of other studies<sup>15,19</sup>.

As for clinical features, our sample of TRD patients showed significantly later onset of MDD, longer duration of illness and more lifetime MDEs compared to nTRD subjects, while most studies did not find such variables to be associated with treatment resistance<sup>15,16,19</sup>. These findings can be seen as a consequence of how TRD patients resulted significantly older than nTRD subjects in our sample, thus increasing duration of illness and number of recurrences.

A peculiar correlation emerged between TRD and family history for suicide and psychiatric disorders, mood disorders in particular. This finding does not match with results of previous studies that showed how the presence of suicide history and psychiatric disorders in first and second-degree relatives were not predictive factors for unresponsiveness to treatment<sup>17-19</sup>. Furthermore, a specific association between TRD and family history of bipolar disorder did not emerge in our sample. This result may suggest that patients with bipolar disorder had been successfully ruled out from the study sample, since bipolar disorder is highly characterized by specific family history and it is generally considered a cause of resistance to AD therapies<sup>34</sup>.

Concerning specific depressive symptoms, we found a statistically significant association between melancholic symptoms and TRD, in agreement with previous data<sup>18</sup>. Moreover, we also found higher severity of depressive symptoms in TRD patients, that do not represent a risk factor for resistance according to the literature<sup>15,19,20</sup>.

Data regarding suicidality is also of interest. In our sample no significant correlation emerged between TRD and suicidality, while other studies reported how current suicide attempts and history of lifetime attempts are both predictive of lack of response to therapies<sup>13,18</sup>. The main reason for this discrepancy may be that we did notice a high current suicide attempts rate in both subsamples (16.0 and 21.0% in TRD and n-TRD respectively), since, contrarily to previous studies, subjects enrolled were all patients in acute phase admitted to our Psychiatric Inpatient Unit. Furthermore, such unexpected finding may be related, again, to careful exclusion of patients with bipolar disorder, since patients with unipolar depression show significantly less suicidality compared to bipolar subjects<sup>35</sup>.

There were lower comorbid psychiatric diseases in patients with TRD, although no differences were noticed in relation to specific diseases (e.g. personality disorders, alcohol/drug use disorders, anxiety disorders and obsessive-compulsive disorder). This data is not consistent with most of previous papers, which associated a higher rate of treatment resistance with anxiety disorders<sup>16</sup> and substance use disorders<sup>18</sup>, while the correlation with personality disorders showed mixed results<sup>23,24</sup>. However, such diseases often present diagnostic issues that may have led to difficulties in carrying out optimal therapeutic strategies, with consequent misvaluation of TRD rates. Furthermore, our sample included only patients with MDD as principal diagnosis. Medical comorbidities were also related to treatment resistance in our sample, in accordance with the literature<sup>25</sup>. In particular, our data showed a significantly higher rate of hypothyroidism (23.5%) in TRD patients, as described in previous works<sup>26</sup>.

Regarding pharmacological treatments at discharge, our analysis showed that TRD patients are prescribed more medication (both psychiatric and overall), most likely in relation to the higher number of medical comorbidities. A significant trend emerged in using SNRIs but not SSRIs, as the latter pertain to first-line treatments, which TRD patients often show resistance to. We registered a higher prescription of antipsychotics (in particular quetiapine and aripiprazole) and lithium in TRD,

while use of benzodiazepines was significantly lower, possibly due to add-on therapy with quetiapine being very frequent in TRD subsample. In fact, add-on was the primary therapeutic strategy as it was employed in almost half of TRD patients (48.1%), whereas switch to another AD was the least used strategy. Such findings are likely influenced by the study setting (psychiatric ward with inpatients only); TRD patients were therefore in need of valid and immediately effective therapeutic options in order to obtain symptomatic remission in a very short timespan (few days of hospitalization).

Our study presents several limitations, mainly due to the retrospective design of the study. Firstly, our work did not include a follow up program after discharge, which would have allowed us to monitor long-term effectiveness of medication and therapeutic options instituted during hospitalization. Another limitation concerns the fact that therapeutic strategies are often conditioned by the clinician's experience and expertise, thus also influencing treatment options. Moreover, no treatment alternative to pharmacological treatments have been applied (e.g. sleep deprivation, light therapy, psychotherapy, somatic treatments). On the other hand, subjects enrolled for this study were real-world inpatients with MDD, contrarily to most studies conducted on outpatients.

In conclusion, the present study found that the TRD is a very frequent conditions in acute psychiatric wards, representing one-third of cases of major depressive disorder. We observed several unexpected findings, such as higher severity of symptoms, higher family history for suicide and psychiatric disorders (especially mood disorders) and lower rate of psychiatric comorbidities, that have not been described as predictive factors for TRD in literature. The lack of specific correlation between suicide and TRD is particularly noteworthy and deserving further research. Such clinical findings are strengthened by exclusion of any subtype of bipolar disorder and suggest that TRD can show peculiar characteristics depending on clinical setting. As for psychopharmacological treatments strategies in TRD patients, the lack of valid options highlights the urgent need for new compounds.

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# Clinical differences and associations between women with borderline personality and their partners: an exploratory study

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## SUMMARY

### Introduction

One of the most interesting areas of interpersonal functioning in people with Borderline Personality Disorder (BPD) is their romantic relationships (RR). In this empirical context, our main objective was to identify the principal differences and associations between clinical and relational variables in women with BPD compared with their partners.

### Methods

A cross-sectional, comparative study was carried out on women with BPD ( $n = 23$ ) and their partners ( $n = 23$ ). Clinical and relational variables were measured using the following: the World Health Organization Quality of Life (WHOQOL) instrument, the Rosenberg Self-Esteem scale, the Personality Inventory (NEO PI-R), the Conflict Tactics Scale (CTS), the Communication Patterns Questionnaire (CPQ), the Experiences in Close Relationships scale (ECR), the Dyadic Adjustment Scale (DAS), and the Index of Sexual Satisfaction (ISS). Stepwise MANCOVA, MANOVA and Pearson correlates were performed.

### Results

Partners scored significantly higher than did women with BPD on social relationships ( $F = 6.08, p = .01$ ), self-esteem ( $F = 12.90, p < .001$ ), agreeableness ( $F = 12.19, p < .001$ ), conscientiousness ( $F = 14.00, p < .001$ ), avoidant communication style ( $F = 72.78, p < .001$ ), cohesion ( $F = 10.09, p < .001$ ), and affection ( $F = 72.20, p < .001$ ). Conversely, BPD women scored significantly higher than their partners did on demanding communication ( $F = 278.76, p < .001$ ), consensus ( $F = 62.36, p < .001$ ), emotional satisfaction ( $F = 11.08, p < .001$ ), and anxious attachment ( $F = 38.94, p < .001$ ). Correlation analyses showed significant positive associations between agreeableness in partners and demanding communication style in BPD women ( $r = .43, p = .03$ ). Likewise, satisfaction in the BPD group was positively associated with conscientiousness in partners ( $r = .53, p = .01$ ).

### Conclusions

Women with BPD and their Partners shown a relational dyadic based on hiperdemanding communication of the BPD and an avoidant and contention pattern of the partner.

**Key words:** borderline personality disorder, romantic relationships, pathological dyadic, partner, intimacy

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### Conflict of interest

The Authors declare no conflict of interest

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## Introduction

Borderline Personality Disorder (BPD) is a severe, chronic mental disorder, with a prevalence of between 2 and 5.9% in community samples and between 15% and 20% in psychiatric outpatient samples<sup>1-4</sup>. Because of the symptomatic heterogeneity of BPD, empirical studies have tended to group BPD into four clusters of interrelated symptoms: emotional deregulation, high impulsivity, identity disturbances, and interpersonal dysfunction<sup>3,5,6</sup>.

In relation to the last cluster mentioned above, interpersonal dysfunction, various longitudinal and cross-sectional studies have shown patients in this group to have a higher number of recurring interpersonal conflicts compared with healthy controls<sup>5-8</sup>. Studies to date have positively associated this interpersonal dysfunction with certain developmental factors, such as childhood traumatic episodes (CTE), insecure attachment, hypomentalizing, and early maladaptive schemas<sup>9-12</sup>.

Such interpersonal dysfunction has its greatest expression in the context of romantic relationships (RRs). In particular, various studies have found positive associations between interpersonal dysfunction and instability in RRs in people with BPD<sup>13</sup>. In addition, it should be noted that a considerable number of emotional relapses treated during psychiatric emergencies and/or hospitalisation are the cause of romantic breakdowns and/or conflicts with partners<sup>14,15</sup>.

Furthermore, longitudinal studies have found that people with BPD have shorter-lasting RRs and a higher number of romantic partners (i.e., through infidelity or promiscuity) compared with healthy controls<sup>8,14-17</sup>. In this same vein, cross-sectional studies have found people with BPD to manifest more maladaptive relational behaviours (i.e., passive-aggressive communication styles, insecure attachment styles, intimate aggression) compared with healthy controls. These behaviours promote a recurring pattern of ruptures-reconciliations<sup>14,18-20</sup>. Moreover, other cross-sectional and longitudinal studies have reported that some clinical characteristics of people with BPD (i.e., the presence of CTE, low self-esteem, low social cognition) are positively associated with marital aggression and ultimately the break-up of RRs compared with samples with no BPD<sup>14,21-25</sup>.

As for aggressive behaviour in RR, a number of cross-sectional and longitudinal studies have found a positive association between aggression and various typical BPD symptoms (i.e., emotional deregulation, impulsivity, depressive mood)<sup>14,26,27</sup>. That is, compared with healthy controls, people with BPD have been found to exhibit more aggressive behaviours (i.e., physical, verbal, psychological aggression) towards their partners<sup>14,28,29</sup>. For example, one four-month longitudinal follow-up study reported that 37% of partners of people with BPD were victims of physical or psychological aggression<sup>30</sup>. Similarly, other studies have found between 20 and 60% of partners of people with BPD to experience physical aggression, 80% verbal aggression<sup>14,29</sup>. Finally, other research has shown a positive association between aggression (i.e., hostility, physical and/or verbal aggression) and emotional and sexual dissatisfaction in RRs<sup>14,30</sup>.

Regarding the clinical profile of partners of people with BPD, an 18-month follow-up study found that these

partners exhibited a greater number of maladaptive behaviours (i.e., greater physical aggression, avoidant communication style, avoidant attachment style) than did partners of people without BPD<sup>14</sup>. Some studies have also reported a higher incidence of personality disorders (paranoid, obsessive-compulsive and avoidant disorders) in the partners of people with BPD compared with partners of people without BPD<sup>14,31,32</sup>.

The findings presented in this paper are based on a comparative clinical framework involving BPD patients and healthy controls. However, empirical study of the clinical profile of partners of people with BPD is in an emerging context<sup>14,16</sup>. Thus far, previous studies have failed to generate robust results on associations and differences in relational and clinical variables between people with BPD and their partners.

In this empirical context, the overall objective of the study was to determine the main clinical differences between people with BPD and their partners. Specifically, the objectives were: i) to identify differences in clinical variables between people with BPD and their partners, in terms of quality of life, self-esteem, and personality dimensions; ii) to elucidate differences in relational variables between people with BPD and their partners, in terms of communication style, attachment style, and emotional and sexual satisfaction; and iii) to determine the associations between the clinical and relational variables of people with BPD and their partners.

## Methods

### Participants

Potentially eligible participants were initially referred to us by their clinicians as they consecutively attended the Adult Outpatient Mental Health Centre in Mataró (Barcelona, Spain) from December 2016 to May 2018. The inclusion criteria for the BPD group were meeting the diagnostic criteria for BPD according to the DSM-5<sup>1</sup>, being aged 18-65 years, and, in accordance with similar studies, having been in an RR for twelve months or having lived with their partner for four months<sup>14,16,33</sup>. The exclusion criteria for the BPD group were the following: i) having lifetime comorbidity with a schizophrenia spectrum disorder and/or pervasive developmental disorder, according to DSM-5; ii) having a diagnosed intellectual disability (IQ < 70), as not ed in their clinical records; and iii) having any idiomatic barriers to reading/speaking Spanish or Catalan languages. Because of the considerable prevalence of substance misuse among BPD patients, only those who showed symptoms of intoxication or substance withdrawal at the time of assessment were excluded. Of the 27 potentially suitable outpatients, two declined to participate, mainly because they did not want to

answer sensitive questions in the questionnaires. Another two patients did not meet the lifetime criterion for BPD but had borderline traits. Hence, the final sample comprised 23 participants in total: 23 BPD women and their 23 partners (see Figure 1).

Participants individually attended one session of two hours, on average, in order to complete the administered questionnaires and semi-structured interviews. All the participants (women with BPD and their partners) were interviewed directly by the authors of this paper, all of who are doctoral-level clinicians or clinical psy-

chologists and widely experienced in personality disorders. All three were also trained in conducting the assessment. The degree of agreement between interviewers on BPD diagnoses was high (*Cohen's Kappa* = .87). One week later, participants completed self-administered questionnaires in a second session, with the interviewers on hand to answer any questions they might have. The study was approved by the hospital's Institutional Review Board, and informed consent was obtained from all patients after being given a full explanation of the nature of the study.

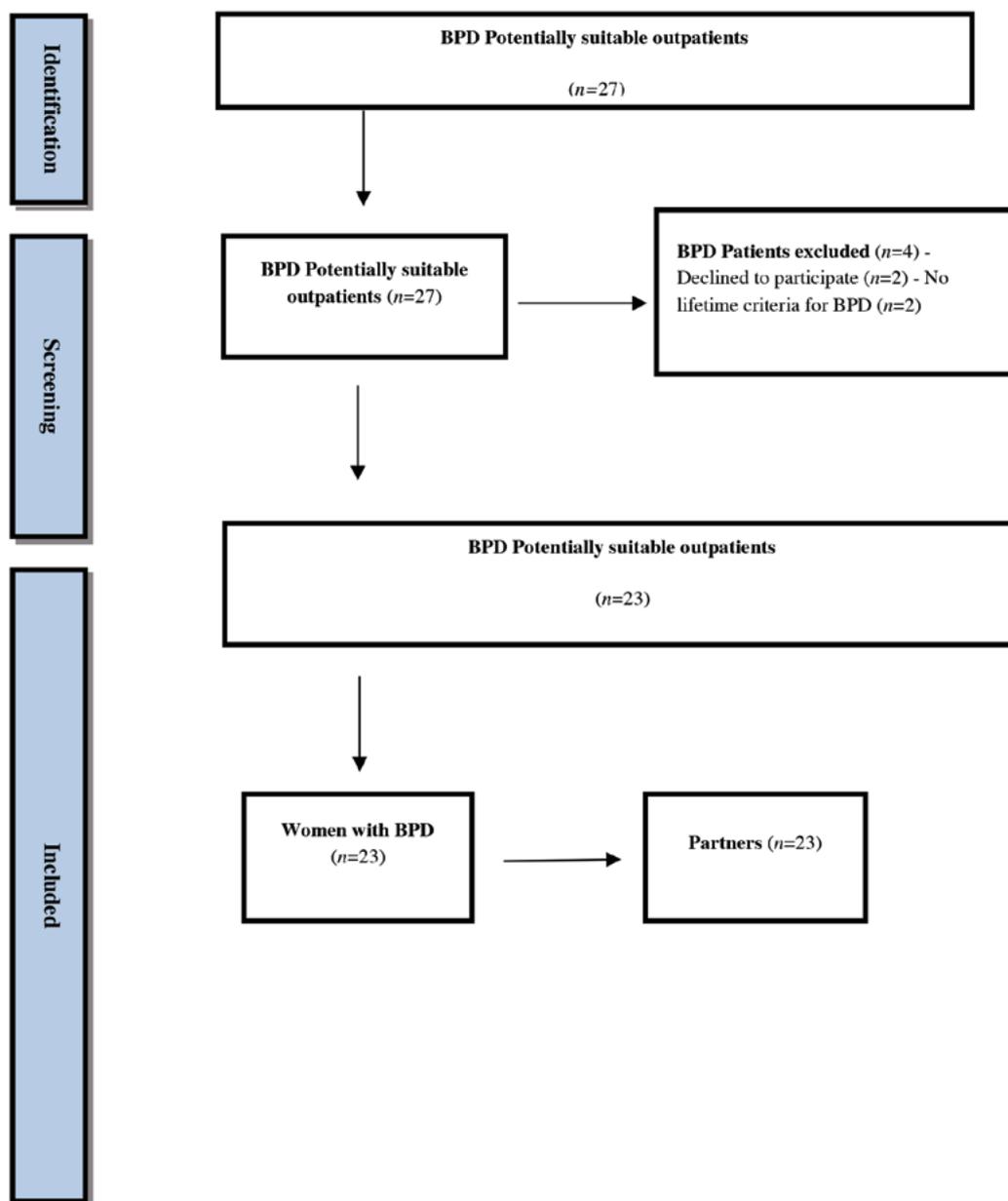


FIGURE 1. Flow-chart of study selection.

## Instruments

Demographic information was collected using an ad hoc questionnaire, as well as via interviews with participants when such information was either no longer available in their clinical records or was contradictory.

### *Instruments for women with BPD and their partners*

**Personality Dimensions.** The Personality Inventory NEO (NEO-PI-R)<sup>34</sup>. This self-administered questionnaire measures personality dimensions. Validation of the Spanish version showed it to have adequate internal consistency (*Cronbach's alpha* = .60 to .90).

**Depressive Mood.** Beck's Depression Inventory (BDI)<sup>35</sup>. Validation of the Spanish version showed it to have adequate internal consistency (*Cronbach's alpha* = .90), proving it to be a reliable instrument for assessing the severity of depressed mood.

**Quality of Life and Self-Esteem.** The Spanish version of the World Health Organization Quality of Life, Short-Form (WHOQOL-BREF)<sup>36</sup> was used to measure quality of life and showed adequate internal consistency (*Cronbach's alpha* > .80); self-esteem was measured using the Spanish version of the Rosenberg Self-esteem (RSE) scale<sup>37,38</sup>, which also showed adequate internal consistency (*Cronbach's alpha* = .87).

**Attachment Style.** The Experiences in Close Relationships scale (ECR-R)<sup>39,40</sup>. The ECR-R has two dimensions: anxiety and avoidance. Validation of the Spanish version showed it to have adequate internal consistency (*Cronbach's alpha* > .65).

**Communication Patterns.** The Communication Patterns Questionnaire (CPQ)<sup>41,42</sup>. This has three scales: the mutual constructive communication scale; the mutual avoidance communication scale; and the demand/withdraw communication scale. Validation of the Spanish version showed it to have adequate internal consistency (*Cronbach's alpha* > .75).

**Intimate Aggression.** The Conflict Tactics Scale (CTS-2)<sup>43</sup>. This 39-item self-report instrument measures levels of intimate violence in an RR. It has four scales: negotiation; physical aggression; sexual cohesion; and injuries. Validation of the Spanish version showed it to have adequate internal consistency (*Cronbach's alpha* = .88).

**Emotional and Sexual Satisfaction.** The Dyadic Adjustment Scale (DAS)<sup>45,46</sup>. The DAS was used to assess satisfaction with relationships. Validation of the Spanish version showed it to have adequate internal consistency (*Cronbach's alpha* > .80). The Sexual Satisfaction Index (SSI)<sup>47,48</sup> provided an overall score of sexual dysfunction. Validation of the Spanish version showed it to have adequate internal consistency (*Cronbach's alpha* = .76 to .86).

**Social Cognition.** The Interpersonal Reactivity Index (IRI)<sup>49</sup>. This measure has four subscales: Perspective-Taking, Fantasy, Empathic Concern, and Personal Distress. Validation of the Spanish version showed it

to have adequate internal consistency (*Cronbach's alpha* > .70).

### *Instruments for women with BPD only*

**Personality Disorder Diagnosis.** Personality Disorders (SCID 5 – PD)<sup>49</sup>. The original version in English was translated into Spanish and later revised by a native Spanish speaker (bilingual) with knowledge of psychology. Here, a semi-structured interview is used to diagnose BPD. The Spanish version showed adequate internal consistency (*Cronbach's alpha* = .81).

## Statistical analysis

Depending on the nature of the variables, the chi-square test, Mann-Whitney U test, ort-test was used to analyse the sociodemographic data. The Shapiro-Wilk test was then used to confirm the normal distribution of the quantitative clinical data for both clinical groups.

An initial analysis of covariance (MANCOVA) was performed using depressive mood and social cognition as covariates to observe their effect on variance in the BPD patients group and that of their partners.

A MANOVA was then performed, this time to compare the psychopathological and relational variables of the patients and their partners. As a measure of effect size, the partial eta square (small > .02, medium > .05, large > .08) was calculated ( $p < .05$  being used to denote a significant univariate contrast). Pearson correlations were performed to identify possible associations between the most relevant variables for the patients and their partners. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows, Version 23.0).

## Results

### **Sociodemographic differences between women with BPD and their partners**

The groups differed statistically only on occupation, where a higher level of active employment was apparent in the partners group ( $p < .05$ ). A MANCOVA revealed no statistically significant differences for the variables depressive mood or social cognition ( $p < .05$ ) (see Table I).

### **Clinical differences between women with BPD and their partners**

Clinical differences between women with BPD and their partners are shown in Table II.

One MANOVA revealed statistically significant differences between the two groups for quality of life and self-esteem ( $F = 33.22$ ,  $p = .00$ , *Wilks's lambda* = .22). The univariate analysis showed that the partners group scored significantly higher on social relationships and self-esteem ( $p < .05$ ). Effect sizes were small, the power moderate to high.

**TABLE I.** Sociodemographic comparison between BPD women and their partners.

	Women with BPD (n = 23) n (%)	Partner (n = 23) n (%)	Statistics $\chi^2 / t / F$	P
<b>Age (mean/SD)</b>	38.65 (6.46)	40.42 (9.23)	t = -.86	.23
<b>Education level</b>	4 (18.20)	1(3.30)	$\chi^2 = 6.58$	.08
– No studies	4 (18.20)	6 (27.30)	-	-
– Primary	8 (31.80)	10(53.60)	-	-
– Secondary	7 (31.80)	5 (15.80)	-	-
University			-	-
<b>Occupation</b>	3 (13.60)	2 (8.70)	$\chi^2 = 3.83$	.03*
– Student	6 (27.30)	18 (78.30)	-	-
– Employee	5 (22.70)	2 (8.70)	-	-
– Unemployed	4(22.71)	1 (4.30)	-	-
– Retired due to disability	3 (13.60)	0 (.00)	-	-
Medical leave			-	-
<b>Children (mean/SD)</b>	.87 (.81)	.80 (.76)	t = -.07	.94
<b>BDI (mean/SD)</b>	22.64 (5.90)	19.06 (4.28)	F = 1.24	.23
<b>IRI (mean/SD)</b>				
– Fantasy	11.82 (4.65)	10.00 (4.46)	F = 1.24	.22
– Perspective Tacking	10.76 (6.36)	13.77 (6.59)	F = .94	.35
– Empathic Preoccupation	9.80 (4.45)	9.62 (6.39)	F = .08	.93
– Personal Distress	9.06 (4.91)	6.46 (40.25)	F = 1.79	.08

BPD: Borderline Personality Disorder; SD: Standard Deviation

\*\*p &lt; .00 in women with BPD vs partner

\*p &lt; .05 in women with BPD vs partner

**TABLE II.** Psychopathological comparison among clinical variables between BPD women and their partners.

	Women with BPD (n = 23) M (SD)	Partner (n = 23) M (SD)	Statistics F	P	$\eta^2$	P
<b>WHOQOL</b>						
– Physical health	16.45 (4.76)	11.53 (6.10)	.75	.39	.15	.56
– Psychological health	13.30 (3.35)	7.76 (5.33)	1.71	.19	.17	.65
Social relationships	8.60 (4.53)	28.65 (9.99)	6.08	.01*	.21	.87
Environment	17.80 (5.43)	16.28 (4.89)	.14	.70	.10	.32
Self-esteem	16.40 (3.99)	27.10 (10.90)	12.90	.00**	.75	.93
<b>NEO PIR</b>						
– Neuroticism	109.10 (28.07)	138.53 (25.12)	12.10	.00**	.24	.92
– Extraversion	102.71 (35.04)	138.68 (22.59)	14.52	.00**	.28	.96
– Openness	104.95 (33.84)	126.42 (33.39)	4.06	.07	.20	.50
– Agreeableness	93.76 (37.74)	133.68 (34.19)	12.19	.00**	.39	.92
– Conscientiousness	104.00 (35.33)	145.47 (34.62)	14.00	.00**	.43	.95

BPD: Borderline Personality Disorder; NEO PIR: Neuroticism Extraversion Openness Personality Inventory Revised; SD: Standard Deviation; WHOQOL: World Health Organization Quality of Life

\*\*p &lt; .00 in women with BPD vs partner

\*p &lt; .05 in women with BPD vs partner

Another MANOVA also revealed statistically significant differences between the personality dimensions ( $F = 7.23, p = .00, Wilks \lambda = .48$ ). The univariate analysis showed that the partners group scored significantly higher on neuroticism, extraversion, agreeableness, and conscientiousness compared with the BPD group ( $p < .05$ ). Effect sizes were medium to large, the power high.

### Relational differences between women with BPD and their partners

The relational differences between women with BPD and their partners are shown in Table III.

One MANOVA showed statistically significant differences between the communication style variables ( $F = 129.02, p = .00, Wilks \lambda = .08$ ). The univariate analysis revealed that the partners group scored significantly higher on avoidant communication compared with the BPD group ( $p < .05$ ). Conversely, the BPD group scored significantly higher on demanding communication style ( $p < .05$ ). Effect sizes were small, the power high.

Another MANOVA revealed no statistically significant differences between the variables of intimate aggression ( $F = 2.92, p = .08, Wilks \lambda = .56$ ). Similarly, the univariate analysis showed no significant differences between the two groups.

A further MANOVA did reveal statistically significant differences between the attachment style variables ( $F = 2.38, p = .00, Wilks \lambda = .35$ ). The univariate analysis showed that the BPD group scored significantly higher on anxious attachment compared with the partner group ( $p < .05$ ). Effect sizes were small, the power moderate to high.

The final MANOVA revealed statistically significant differences between the variables for emotional satisfaction and sexual satisfaction ( $F = 281.71, p = .00, Wilks \lambda = .03$ ). Regarding emotional satisfaction, the BPD group presented significantly higher scores on consensus and satisfaction ( $p < .05$ ). In contrast, the partners group showed significantly higher scores on cohesion and affection ( $p < .05$ ). The effect sizes were small, the power moderate to high. For sexual satisfaction, the univariate analysis showed no statistically significant differences ( $p > .05$ ).

### Associations between clinical variables and relational variables

#### *Associations between clinical variables and relational variables in women with BPD and their partners*

Associations between clinical variables and relational variables in women with BPD and their partners are shown in Table IV. The correlation analysis revealed sig-

**TABLE III.** Clinical differences in relational variables between BPD women and their partners.

	Women with BPD (n = 23) M (SD)	Partner (n = 23) M (SD)	Statistics F	P	$\eta^2$	P
CPQ						
– Constructive com.	23.96 (9.65)	25.61 (18.44)	.13	.71	.00	.06
– Avoidant com.	24.17 (6.61)	72.78 (29.24)	59.90	.00**	.25	1.00
Demanding com.	85.30 (18.31)	10.56 (5.48)	278.76	.00**	.26	1.00
CTS						
– Med. physical aggression	24.40 (41.40)	32.78 (10.64)	.69	.40	.05	.12
– Psychological aggression	15.28 (43.23)	32.56 (12.83)	2.68	.10	.11	.36
– Physical grave aggression	12.20 (42.96)	23.56 (5.22)	1.19	.28	.06	.18
Argumentation	13.48 (43.48)	14.00 (6.60)	.00	.96	.02	.05
ECR						
– Anxious attachment	36.39 (6.73)	7.84 (5.29)	38.94	.00**	.31	1.00
– Avoidant attachment	38.13 (4.22)	39.17 (12.22)	.16	.69	.01	.06
DAS						
Consens	41.09 (11.44)	21.11 (14.10)	62.36	.00**	.26	1.00
– Satisfaction	26.96 (7.23)	20.41 (4.19)	11.08	.00**	.02	.090
– Cohesion	13.74 (5.26)	18.71 (4.31)	10.09	.00**	.19	.87
– Affection	8.57 (3.48)	75.53 (11.75)	72.20	.00**	.19	1.00
– DAS Total	85.87 (17.13)	84.57 (19.06)	.20	.88	.00	.05
ISS Total	63.99 (11.02)	49.20 (11.09)	2.84	.10	.11	.45

BPD: Borderline Personality Disorder; CPQ: Communication Patterns Questionnaire; CTS: Conflict Tactics Scale; ECR: Experience Close Relationship; DAS: Dyadic Adjustment Scale; ISS: Index Sexual Satisfaction; SD: Standard Deviation

\*\* $p < .00$  in women with BPD vs partner

\* $p < .05$  in women with BPD vs partner

**TABLE IV.** Associations between clinical variables and relational variables of Women with BPD and their partners.

Partner variables (n = 23) <i>r/(p)</i>	Womenwith BPD (n = 23)			
	Demanding com.	Anxious attachment	Consens	Satisfaction
Neuroticism	.70 (.77)	.37 (.20)	-.13 (.58)	-.32 (.16)
Extraversion	.37 (.11)	.07 (.74)	.04 (.95)	.13 (.57)
Agreeableness	<b>.47 (.03)*</b>	.26 (.26)	.15 (.52)	-.06 (.79)
Conscientiousness	-.01 (.96)	.28 (.22)	.09 (.70)	<b>.53 (.01)*</b>
Social relationships	-.19 (.58)	-.24 (.49)	.12 (.72)	-.46 (.17)
Self-esteem	-.11 (.65)	-.09 (.70)	-.02 (.93)	.35 (.15)
Affection	.31 (.20)	-.41 (.07)	.34 (.15)	-.35 (.15)

BPD: Borderline Personality Disorder

\*\* $p < .00$ .

\* $p < .05$ .

nificant positive associations between the dimensions of agreeableness in the partners group and demanding communication style in the BPD group ( $r = .43$ ,  $p = .03$ ). Likewise, satisfaction in the BPD group was positively associated with conscientiousness in the partners group ( $r = .53$ ,  $p = .01$ ).

#### *Associations between clinical variables and relational variables in partners*

Correlation analysis showed significant positive associations between psychological health and satisfaction in partners ( $r = .72$ ,  $p = .02$ ). In addition, a higher score on social relations was positively associated with affect ( $r = .70$ ,  $p = .03$ ).

## Discussion

The primary objective of this research was to determine the main clinical differences and associations in clinical and relational variables between people with BPD and their partners (see Figure 2). Overall, one of our most significant results was that their RRs were more satisfying for the women with BPD than for their partners. The lower satisfaction of partners is particularly important, given that their psychological health showed a significant positive correlation with emotional satisfaction. These findings are in contrast with the results of other studies that have reported higher emotional satisfaction in non-BPD partners compared with BPD partners in an RR<sup>14,16</sup>. However, it is important to stress that our study measured differences and associations between RR members in comparison with other comparative studies<sup>14,16</sup>.

Additionally, the fact that the partners of women with BPD scored significantly higher on the social relation-

ships variable suggests that they may form other types of interpersonal attachments. These other social relationships may give them personal satisfaction, given their reported dissatisfaction in their RR<sup>14,33</sup>. If so, in psychotherapeutic work with partners of patients with BPD, consolidating other social attachments may be a protective factor against potential burn-out caused by living with a person with BPD. These findings are consistent with those of a cross-sectional study that found partners in RRs to report a higher number of social relationships, compared with their BPD partner<sup>33</sup>.

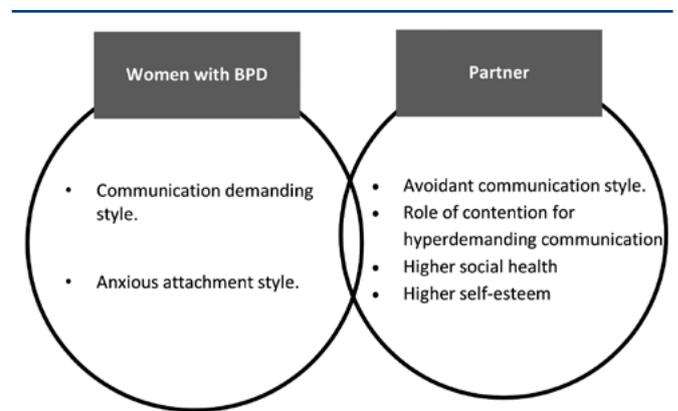
Another interesting finding of this study was that women with BPD had a significantly more demanding communication style, while their partners displayed amore avoidant communication style. Furthermore, there was a significant positive correlation between the two variables. These findings are consistent with those of a longitudinal study examining BPD samples<sup>14</sup> and provide tentative evidence of a transactional (not merely "intra-psychic") origin of the relational psychopathology of a person with BPD in an RR. Thus, a solid and dysfunctional attachment seems to develop, whose equilibrium is based on the principle of a pathological dyadic comprising both members. In relation to the potential clinical characteristics that could be modulating this dysfunctional dyadic, the partners in the present study scored significantly higher than their BPD partners did on the personality dimensions of agreeableness and conscientiousness, as well as on the variable affection.

Patients with BPD scored significantly higher than their partners did on anxious attachment. Taken together, these results suggest that the relational dyadic operates on the basis of clearly fixed roles within an interdependency: a more emotionally demanding tendency (hyper-demanding) on the part of the BPD patient; and a ten-

dency to be more emotionally contained, on the part of their partners. However, we cannot state conclusively whether these roles actually represent the “states” or “traits” of those involved in the RR, since the data were self-reported and cross-cutting in nature. Longitudinal studies are therefore necessary, preferably with a more ecological evaluation methodology based primarily on observational records<sup>14,17,33</sup>.

A number of clinical implications for psychotherapeutic treatment arise from the findings of this research. First, our results support approaches such as systemic partner interventions or behavioural family therapy for patients with BPD<sup>41</sup>. Likewise, the use of cognitive-behavioural techniques to work on co-dependence and assertiveness in the partners of patients with BPD would be justified<sup>41</sup>. However, it is important to stress that not all patients with BPD will be susceptible to these types of therapeutic interventions. Rather, this intervention framework should be limited to BPD patients in RRs that have been stable for a period of time (for at least 12 months) and who are motivated to change, and where both members of the RR comprise a pathological dyadic<sup>41</sup>.

This study has various limitations that should be considered. First, since it is a cross-cutting study, causal relationships between the psychopathology of women with BPD and relational variables of their RRs cannot be established. In this sense, it is not possible to know the current romantic status of the participants. Second, the sample size was small and thus the generalisation and reliability of our results are limited. Third, the partners of the participants with BPD were not assessed at the categorical level (psychiatric disorders of Axis I and



**FIGURE 2.** Relational dyadic between women with BPD and their partners.

Axis II). And finally, only self-administered instruments of a dimensional nature were used.

In conclusion, further longitudinal and cross-sectional studies of the RRs of people with BPD are needed. Specifically, it would be useful to know the incidence of Axis I and Axis II psychiatric disorders, childhood trauma, and early maladaptive schemas in samples of people with BPD and their partners. Such clinical data could prove useful in elucidating a relational pattern between people with BPD and their partners (Fig. 2).

### Ethical statements

Authors declare that all subjects have given their informed consent and the study protocol has been approved by the investigation ethical committee of Hospital of Mataro, Barcelona.

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# James Bond villains and psychopathy: a literary analysis

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## SUMMARY

### Objective

Psychopathy is a construct used to describe individuals without a conscience, who knowingly harm others via manipulation, intimidation, and violence, but feels no remorse. In consideration of the intriguing nature of the psychopathy construct, it is not surprising that a number of psychopathic characters have been portrayed in popular culture, including modern literature. We set out to systematically review Ian Fleming's James Bond novels to assess the presence of psychopathic traits in the characters of Bond villains.

### Methods

We reviewed the full-text of a representative sample of seven novels published by Fleming between 1954 and 1965 ('Live and let die', 'Dr. No', 'Goldfinger', 'Thunderball', 'On Her Majesty's secret service', 'You only live twice', and 'The man with the golden gun'), portraying the fictional characters of six villains. For each villain, we extracted examples of quotations that demonstrate the presence of specific psychopathic traits from the Psychopathy Checklist-Revised (PCL-R).

### Results

We found ample evidence of the presence of specific psychopathic traits from the PCL-R in James Bond villains. The most commonly observed psychopathic trait is callousness/lack of empathy, which is portrayed by all the examined characters of villains. Contrary to Bond, the villains are consistently described as having physical monstrosity, in addition to their psychopathic traits.

### Conclusions

The villains' psychopathic traits appear to be functional to Fleming's narrative scheme, that revolves around the Bond-villain (Good/Evil) dichotomy. However it has been suggested that this dichotomy is only partial, as a few psychopathic traits appear to be shared by Bond himself. Despite the difficulties of implementing literature in the curriculum of medical students and psychiatry trainees, a healthy interest in literature and art could be beneficial for its educational value and should be encouraged, possibly in the form of book clubs.

**Key words:** Ian Fleming, James Bond, literary analysis, novels, psychopathy, villains

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### Conflict of interest

The Authors declare no conflict of interest

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## Introduction

The first medical description of the phenomenon we recognise today as psychopathy was provided by French psychiatrist Philippe Pinel (1745-1826), who referred to it as 'manie sans délire' ('mania without delirium'). Pinel used this term to describe individuals who maintained the capacity for rational thought but nevertheless sometimes acted 'under the dominion of instinctive and abstract fury, as if the active faculties alone sustained the injury'<sup>1</sup>. The scientific study of the individual without a conscience, who knowingly harms others but feels no remorse, flourished in the second half of the nineteenth century and included speculations by the Italian crimi-

nologist Cesare Lombroso, who claimed to have found evidence for the existence of an 'inborn criminal' ('delinquente nato') in anatomical abnormalities<sup>2</sup>. Throughout the first half of the twentieth century, although the labels 'psychopathic inferiority' and 'sociopathic personality disturbance' were applied widely to antisocial types, the concept of psychopathy resisted standard definition<sup>3</sup>. During the second half of the twentieth century, the competing terms 'psychopathy', 'sociopathy', and 'antisocial personality disorder' gained currency among mental health professionals whose clinical descriptions of the social and emotional traits associated with conscienceless individuals became increasingly more precise. However it was not until the end of the twentieth century, with the development of the Hare Psychopathy Scales (especially the widely used Psychopathy Checklist-Revised, PCL-R), that psychopathy became a well-defined and accepted clinical syndrome<sup>4,5</sup>. In the early twenty-first century, the term 'psychopathy' gained general ascendancy over its rivals in clinical discourse, and the label is now applied, as the forensic psychologist Hugues Hervé framed it, to individuals 'instrumentally impulsive individuals with poor behavioral controls who callously and remorselessly bleed others for purely selfish reasons via manipulation, intimidation, and violence'<sup>6</sup>.

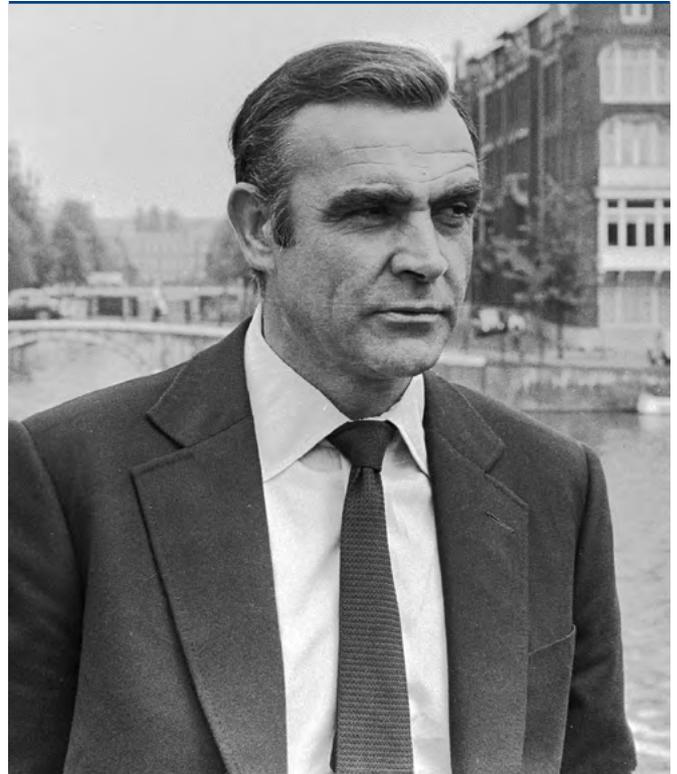
In consideration of the intriguing nature of the psychopathy construct, it is not surprising that a number of psychopathic characters have been portrayed in popular culture. For example, Thomas Harris' 1988 novel 'The silence of the lambs' (transposed into a famous film of the same name in 1991) featured the fictional character of Hannibal Lecter, a psychopathic killer portrayed as an individual with superior intelligence, a quality that enhanced his ability to manipulate and victimize others<sup>7</sup>. Literary portrayals of psychopathic personalities can be consistent with scholarly research to different degrees. British author Ian Fleming (1908-1964) created one of the literary and cinematic icons of the twentieth century, secret agent 007 James Bond (Fig. 1)<sup>8</sup>.

Between 1953 and 1965 Fleming published 13 novels focusing on the endless fight between James Bond and a series of famous villains, whose larger-than-life characters made memorable appearances in the successful series of James Bond films (Fig. 2)<sup>9,10</sup>.

Interestingly, many of these villains appear to portray psychopathic traits. We set out to review the text of a representative sample of Fleming's novels in order to assess the presence of psychopathic traits in Fleming's descriptions of James Bond villains.

## Methods

We reviewed the full-text of a representative sample of seven James Bond novels published by Ian Fleming between 1954 and 1965: 'Live and let die' (1954), 'Dr. No'



**FIGURE 1.** Sean Connery playing James Bond in the successful film series (1971).

(1958), 'Goldfinger' (1959), 'Thunderball' (1961), 'On Her Majesty's secret service' (1963), 'You only live twice' (1964), and 'The man with the golden gun' (1965). We focused our analysis on Fleming's descriptions of the villains, i.e. James Bond main antagonists: Mr. Big ('Live and let die'), Dr. No ('Dr. No'), Goldfinger ('Goldfinger'), Emilio Largo ('Thunderball'), Blofeld ('On Her Majesty's secret service' and 'You only live twice'), and Scaramanga ('The man with the golden gun'). For each villain, we extracted examples of quotations that demonstrate the presence of specific psychopathic traits from the PCL-R<sup>11,12</sup>. The PCL-R consists of 20 items tapping into the main psychopathic traits and is split into two broad factors (Tab. I).

Factor 1 encompasses interpersonal and affective traits, whereas factor 2 captures behaviours that are antisocial, impulsive, and related to an unstable lifestyle. Three further items do not fall into either of these categories: committing a wide variety of crimes, having many short-term marital relationships, and displaying a promiscuous sexual behaviour. In clinical/forensic settings, each item of the PCL-R is scored 0 (not present), 1 (partially or possibly present) or 2 (present), with a score of 30 or above suggesting a diagnosis of psychopathy.



FIGURE 2. Ian Fleming's James Bond novels.

## Results

### Mr. Big

Mr. Big is James Bond's main antagonist in Ian Fleming's novel 'Live and let die' (1954)<sup>13</sup>. The role of Mr. Big was played by American actor Yaphet Kotto in the

1973 film 'Live and let die', in which James Bond was played by Roger Moore. Buonaparte Ignace Gallia gets his nickname Mr. Big from his extraordinary height and bulk, in addition to his initials. Fleming describes him as physically abnormal, as well as intellectually brilliant, with a 'great football of a head, twice the normal size and very nearly round'. Although he does not smoke or drink, he suffers from chronic heart disease, which gives his skin a greyish hue: 'grey-black, taut and shining like the face of a week-old corpse in the river'. As a young boy, Mr. Big was introduced to the world of voodoo. In Haiti, his home nation, Mr. Big started work as truck driver, but soon emigrated to the United States, where he began his criminal enterprises. He owned half the share of a nightclub in Harlem: the person to whom the other half belonged was later found at the bottom of lake. Mr. Big was conscripted for the war in 1943 and worked for the United States military intelligence. After the war, Mr. Big set up a few nightclubs and a chain of brothels. He also built a voodoo temple and spread a rumour that he was in fact a zombie, thus reinforcing his perverse influence over the African-American community. Examples of passages from the novel 'Live and let die' that demonstrate the presence of specific psychopathic traits from the PCL-R in Mr. Big are presented in Table II.

### Dr. No

Dr. No is James Bond's main antagonist in Ian Fleming's novel 'Dr. No' (1958)<sup>14</sup>. The role of Dr. No was played by American actor Joseph Wiseman in the 1962 film 'Dr. No', in which James Bond was played by Sean Connery. Fleming describes Dr. No as very tall (1.98 m) and thin. His shaved head is said to be shaped like a 'reverse oil drop', due to its rounded shape, pointed chin, and yellowish tinge of his skin. He is described as having his hair up-rooted, dark eyebrows, smooth cheekbones, thinned nose, and widened mouth. His eyes are without eyelashes and look 'like the mouths of two small revolvers'. Where his hands once were, he wears mechanical pincers. Dr. Julius No was born in Peking. He

TABLE I. Psychopathic traits in Hare's Psychopathy Checklist-Revised (PCL-R).

Factor 1	Factor 2	Other items
Callousness/lack of empathy	Early behaviour problems	Committing a wide variety of crimes
Conning/manipulative behaviour	Impulsivity	Many short-term marital relationships
Failure to accept responsibility for actions	Irresponsibility	Promiscuous sexual behaviour
Glibness/superficial charm	Juvenile delinquency	
Grandiose sense of self-worth	Lack of realistic long-term goals	
Lack of remorse or guilt	Need for stimulation/proneness to boredom	
Pathological lying	Parasitic lifestyle	
Shallow affect	Parole/probation violations	
	Poor behavioural control	

**TABLE II.** Examples of quotations from Ian Fleming's novel 'Live and let die' (1954) that demonstrate the presence of specific psychopathic traits from the PCL-R in Mr. Big.

Quotation	Trait
"'Mr. Big,' said M, weighing his words, 'is probably the most powerful negro criminal in the world'"	<b>Committing a wide variety of crimes</b>
"'He [Mr. Big] had no known vices except women, whom he consumed in quantities'"	<b>Promiscuous sexual behaviour</b>
"'[Mr. Big:] 'Mister Bond, I suffer from boredom. I am a prey to what the early Christians called 'accidie', the deadly lethargy that envelops those who are sated, those who have no more desires'"	<b>Need for stimulation/proneness to boredom</b>
"'[Mr. Big:] 'I am content, for the time being, to be my only judge, but I sincerely believe, Mister Bond, that the approach to perfection which I am steadily achieving in my operations will ultimately win recognition in the history of our times'"	<b>Grandiose sense of self-worth</b>
"'I intend,' said Mr. Big, in a matter-of-fact discursive tone of voice, 'to bind you together to a line streamed from this paravane and to tow you through the sea until you are eaten by sharks'"	<b>Callousness/lack of empathy</b>
"'With this engine,' he [Mr. Big] gestured towards the gun trained on Bond through the desk drawer, 'I have already blown many holes in many stomachs, so I am quite satisfied that my little mechanical toy is a sound technical achievement'"	<b>Lack of remorse/guilt</b>

Abbreviation. PCL-R: Psychopathy Checklist-Revised

was the illegitimate child of a German missionary and a high-born Chinese girl. He was abandoned by his parents and instead was raised by his aunt. Apparently it was the rejection he suffered at the hands of his parents that inspired his self-proclaimed name (Julius was his father's name). Before being smuggled to the United States and settling in New York City, Dr. No had been involved with the Tongs, a Chinese crime syndicate in Shanghai. He was deft in things criminal: arson, theft, conspiracy and, of course, murder. After stealing a million dollars in gold from, Dr. No was tracked down and tortured by the Tongs, who cut off his hands, shot him through the left side of his chest, and left him for dead. Dr. No survived, because he has dextrocardia and his heart is located on the right side of his body. Dr. No subsequently enrolled in medical school in Milwaukee (to see 'what this clay is capable of') and after graduating he used his title to garner the misguided trust of his victims. Eventually, Dr. No moved to a palace of fabulous pomp in Crab Key Island, where he conducted sadistic experiments on humans in the name of 'science'. Examples of passages from the novel 'Dr. No' that demonstrate the presence of specific psychopathic traits from the PCL-R in Dr. No are presented in Table III.

### Goldfinger

Goldfinger is James Bond's main antagonist in Ian Fleming's novel 'Goldfinger' (1959)<sup>15</sup>. The role of Goldfinger was played by German actor Gert Fröbe in the 1964

film 'Goldfinger', in which James Bond was played by Sean Connery. Fleming describes Goldfinger as 1.52 m tall, with a pale, bland face and thin, chiselled lips. He has red hair and peers from under drooping eyelids with piercing China blue eyes. Overall, his body appears to having been 'put together with bits of other people's bodies'. Auric Goldfinger is trademarked by his love of gold. In fact, talking about gold is the only thing that brings expression to his usually expressionless face. Goldfinger's greedy obsession with gold goes so far as to have yellow-bound erotic photographs, and have his lovers painted head to toe in gold so that he can make love to gold. In the novel, AG is a 42-year-old from Riga, Latvia, who emigrated to Britain at the age of 20. Following naturalization as a British citizen, Goldfinger became the richest man in England, although his wealth was not located in English banks, nor did he pay taxes on it, as it was spread as gold bullion across many countries. Goldfinger was the owner of 'Enterprise Auric A.G.' in Switzerland, maker of metal furniture purchased by several airlines. In addition to being a jeweler, a metallurgist, and a smuggler, Goldfinger was the treasurer of SMERSH, the Soviet counterintelligence agency that was James Bond's nemesis. His henchmen included the Korean giant Oddjob, expert in martial arts, and Pussy Galore, leader of a group of performing catwomen. Examples of passages from the novel 'Goldfinger' that demonstrate the presence of specific psychopathic

**TABLE III.** Examples of quotations from Ian Fleming's novel 'Dr. No' (1958) that demonstrate the presence of specific psychopathic traits from the PCL-R in Dr. No.

Quotation	Trait
"The polite mask [of Dr. No] had gone"	<b>Superficial charm</b>
"[Dr. No:] 'I enjoyed the conspiracies, the burglaries, the murders, the arson of insured properties'"	<b>Committing a wide variety of crimes</b>
"[Dr. No:] 'It was a time of torture and murder and arson in which I joined with delight'"	<b>Lack of remorse/guilt</b>
"[Dr. No:] 'It is a rare pleasure to have an intelligent listener [Bond] and I shall enjoy telling you the story of one of the most remarkable men in the world [referring to himself]"	<b>Grandiose sense of self-worth</b>
"[Dr. No:] 'I called myself 'doctor' because doctors receive confidences and they can ask questions without arousing suspicion'"	<b>Conning/manipulative behavior</b>
"[Dr. No:] 'The German experiments on live humans during the war were of great benefit to science. It is a year since I put a girl to death in the fashion I have chosen for you, woman. She was a Negress. She lasted three hours. She died of terror. I have wanted a white girl for comparison'"	<b>Callousness/lack of empathy</b>

Abbreviation. PCL-R: Psychopathy Checklist-Revised

traits from the PCL-R in Goldfinger are presented in Table IV.

### Emilio Largo

Emilio Largo is James Bond's main antagonist in Ian Fleming's novel 'Thunderball' (1961)<sup>16</sup>. The role of Emilio Largo was played by Italian actor Adolfo Celi in

the 1965 film 'Thunderball', in which James Bond was played by Sean Connery. Largo is depicted by Fleming as a large, muscular, olive-skinned, powerful man exuding animal charm, which women find irresistible. His hair is slick with pomade and his profile resembles the profile of a Roman emperor, with a solid jaw and hooked nose, long sideburns, and hairy hands which

**TABLE IV.** Examples of quotations from Ian Fleming's novel 'Goldfinger' (1959) that demonstrate the presence of specific psychopathic traits from the PCL-R in Goldfinger.

Quotation	Trait
"He [Bond] also looked forward to penetrating Goldfinger's highly successful and, on the face of it, highly mysterious method of fleecing Mr Du Pont [during gambling card games]. It was going to be a most entertaining day"	<b>Conning/manipulative behavior</b>
"[Bond to Goldfinger:] 'You're mad! You don't really mean you're going to kill sixty thousand people!' [Goldfinger to Bond:] 'Why not? American motorists do it every two years'"	<b>Callousness/lack of empathy</b>
"[Bond thinking to himself:] 'In what channel did Goldfinger release his vital force? Into getting rich? Into sex? Into power? Probably into all three'"	<b>Promiscuous sexual behaviour</b>
"Goldfinger had, in three minutes flat, got the meeting on his side. Now everyone was looking towards Goldfinger with profound attention [...] Now everyone was hanging on Goldfinger's words as if he was Einstein"	<b>Superficial charm</b>
"[When Goldfinger is talking about gold] For the first time since Bond had known Goldfinger, the big, bland face, always empty of expression, showed a trace of life"	<b>Shallow affect</b>
"He [Goldfinger] had financed the murder of hundreds, perhaps thousands of victims of SMERSH all over the world"	<b>Committing a wide variety of crimes</b>
"'Yes', Goldfinger nodded. 'That is exactly what we are going to do. We are going to burgle fifteen billion dollars' worth of gold bullion...'"	

Abbreviation. PCL-R: Psychopathy Checklist-Revised

are likened to crawling tarantulas. He is supposedly the last survivor of a once eminent Roman family whose legacy he inherited. Fleming describes Largo as a ruthless Neapolitan black marketeer and fence who moved the riskier and more profitable ventures on the international crime scene after five years smuggling from Tangiers and five years masterminding big jewel robberies in the French Riviera. In the novel, Emilio Largo led his cruiser yacht *Disco Volante* and became the second-in-command and eventually successor to Ernst Stavro Blofeld in the global terrorist organisation SPECTRE (an acronym of Special Executive for Counter-intelligence, Terrorism, Revenge, and Extortion). Emilio Largo's heart is made of ice, and his nerves of steel. His ruthlessness is compared to that of Heinrich Himmler, one of the most powerful men in Nazi Germany, as he does not hesitate to torture his mistress Dominetta 'Domino' Vitali for information. She will eventually kill him (before he can finish off Bond) by shooting him with a spear gun. Examples of passages from the novel 'Thunderball' that demonstrate the presence of specific psychopathic traits from the PCL-R in Emilio Largo are presented in Table V.

### Blofeld

Blofeld is James Bond's main antagonist in Ian Fleming's novels 'On Her Majesty's secret service' (1963)

and 'You only live twice' (1964)<sup>17,18</sup>. The role of Blofeld was played by American actor Aristotelis 'Telly' Savalas in the 1969 film 'On Her Majesty's secret service', in which James Bond was played by George Lazenby, and by British actor Donald Pleasence in the 1967 film 'You only live twice', in which James Bond was played by Sean Connery. Blofeld is described by Fleming as a physically massive and powerfully built man, standing 1.91 m and weighing 140 kg, having become flabby with a huge belly. An amateur weightlifter in his youth, Blofeld's weight is now predominantly made up of fat rather than muscle. His hair is a wiry, black crewcut. The eyelashes of his black eyes are silken and could have belonged to a woman, and he lacks earlobes. Ernst Stavro Blofeld was born on 28 May 1908 (which is also Fleming's birthday) in the sea-port town of Gdynia, Poland, to a Greek mother and Polish father. After studying economics and politics at the University of Warsaw, Blofeld capitalized on the imminent World War II by selling copies of top-secret telegrams to Germany and America which he claimed were from a network of spies he was running. Upon the German invasion of Poland, Blofeld fled to Sweden and then to Turkey, whence he sold information to both the axis and the allies. After the war, Blofeld moved temporarily to South America, before

**TABLE V.** Examples of quotations from Ian Fleming's novel 'Thunderball' (1961) that demonstrate the presence of specific psychopathic traits from the PCL-R in Emilio Largo.

Quotation	Trait
"There was a cool brain and an exquisite finesse behind his [Largo's] actions that had always saved him from the herd's revenge - from his postwar debut as head of the black market in Naples, through five lucrative years smuggling from Tangier, five more master-minding the wave of big jewel robberies on the French Riviera..."	<b>Committing a wide variety of crimes</b>
"Largo cannot live without a woman within reach"	<b>Promiscuous sexual behaviour</b>
"Largo was very popular with everyone"	<b>Superficial charm</b>
"[After Largo shot agent No. 10:] Largo put the muzzle of the gun up to his nose and delicately sniffed at it, moving it to and from under the nostrils as if it was some delicious phial of perfume. In the silence, he looked slowly down one rank of faces and up the other. Finally he said softly, 'The meeting is now at an end. Will all members please return to their cabins and look for a last time to their equipment. Food will be ready from now on in the galley. One drink of alcohol will also be available for those who want it. I will detail two crew members to look after the late No. 10. Thank you'"	<b>Lack of remorse/guilt</b>
"[Discussing the torture of a femme fatale:] 'There are certain uses of electricity of which I [No. 5] have knowledge. The human body cannot resist them. If I can be of any service...?' Largo's voice was equally polite. They might have been discussing remedies for a seasick passenger. 'Thank you. I [Largo] have means of persuasion that I have found satisfactory in the past. But I shall certainly call upon you if the case is an obstinate one'"	<b>Callousness/lack of empathy</b>

Abbreviation. PCL-R: Psychopathy Checklist-Revised

founding SPECTRE in Paris. Examples of passages from the novels 'On Her Majesty's Secret Service' and 'You only live twice' that demonstrate the presence of specific psychopathic traits from the PCL-R in Blofeld are presented in Table VI.

### Scaramanga

Scaramanga is James Bond's main antagonist in Ian Fleming's novel 'The man with the golden gun' (1965)<sup>19</sup>. The role of Scaramanga was played by British actor Christopher Lee (Ian Fleming's step-cousin) in the 1974 film 'The man with the golden gun', in which James Bond was played by Roger Moore. Scaramanga is described by Fleming as a 35-year-old tall (1.90 m) and fit man, moderately built with light brown eyes and reddish crew cut hair extended in the form of side burns and complemented by a thin pencil moustache. His hands are large, well-manicured and ambidextrous. He has a third nipple, considered to be a sign of invulnerability and immense sexual prowess. Indeed, his voracious appetite for inflicting pain and suffering on others is matched only by his carnal desire. Francisco Scaramanga's signa-

ture weapon is a golden gun (a golden Derringer pistol). In the novel, the character is nicknamed 'Pistols' Scaramanga, as well as Paco, a Spanish diminutive of Francisco. Of Catalan origin, Scaramanga performed in acts in a circus owned by his father Enrico while a youngster. He developed an attachment to one of the circus elephants, who went on a rampage and was killed by a policeman during the circus visit to Trieste. Scaramanga witnessed the kill and retaliated it by shooting the policeman through the heart. After killing his first victim at the age of 16, Scaramanga made his way to Naples and the United States, where he became an enforcer for the Spangled Mob. He subsequently traversed the world leaving behind him a series of corpses, including several British secret service officers. He finally settled in Havana, Cuba, where he worked as a freelance assassin, often working for Fidel Castro's secret police, in addition to serving as the chief enforcer for the KGB. Examples of passages from the novel 'The man with the golden gun' that demonstrate the presence of specific psychopathic traits from the PCL-R in Scaramanga are presented in Table VII.

**TABLE VI.** Examples of quotations from Ian Fleming's novels 'On Her Majesty's secret service' (1963) and 'You only live twice' (1964) that demonstrate the presence of specific psychopathic traits from the PCL-R in Blofeld.

Quotation	Trait
"[Discussing the disposal of enemies' corpses] Blofeld said, 'The piranhas and the volcanic mud are useful housekeepers. They keep the place tidy.' [Bond:] 'The sea and the sharks are also useful.' [Blofeld:] 'But often the sharks do not complete the job. That spy we put through the Question Room. He was almost intact when his body was found down the coast. The lake would have been a better place for him. We don't want that policeman from Fukuoka coming here too often'"	<b>Lack of remorse/guilt</b>
"[Blofeld:] 'All right, Mister Bond. But I am so sure of my facts that I am now going to kill you with my own hands and dispose of your body without more ado. On reflection, I would rather do it myself than have it done slowly by the guards'"	<b>Callousness/lack of empathy</b>
"Bond dropped his lighted cigarette and left it to smoulder on the carpet. His whole body tensed. He said, 'I suppose you know you're both [Blofeld and fellow villain Irma Blunt] mad as hatters.' [Blofeld:] 'So was Frederick the Great, so was Nietzsche, so was Van Gogh. We are in good, in illustrious company, Mister Bond'"	<b>Grandiose sense of self-worth</b>
"[Blofeld:] 'This project involved the holding to ransom of the Western World by the acquisition by me of two atomic weapons. Where lies the crime in this, except in the Erewhon of international politics?'"	<b>Failure to accept responsibility for actions</b>
"[Blofeld:] 'But there has developed in me a certain mental lameness, a disinterest in humanity and its future, an utter boredom with the affairs of mankind. So, not unlike the gourmet, with his jaded palate, I now seek only the highly spiced, the sharp impact on the taste buds, mental as well as physical, the tickle that is truly exquisite'"	<b>Need for stimulation/proneness to boredom</b>
"Truth of the matter is he's [Blofeld] probably the biggest crook in the world"	<b>Committing a wide variety of crimes</b>

Abbreviation. PCL-R: Psychopathy Checklist-Revised

**TABLE VII.** Examples of quotations from Ian Fleming's novel 'The man with the golden gun' (1965) that demonstrate the presence of specific psychopathic traits from the PCL-R in Scaramanga.

Quotation	Trait
"[Scaramanga] ...is an insatiable but indiscriminate womanizer who invariably has sexual intercourse shortly before a killing in the belief that it improves his 'eye'"	<b>Promiscuous sexual behaviour</b>
"[Scaramanga] At the age of 16 [...] emigrated illegally to the United States where he lived a life of petty crime on the fringes of the gangs until he graduated as a full-time gunman for The Spangled Mob in Nevada..."	<b>Juvenile delinquency</b>
"[Bond to Scaramanga:] '...now look here, Mr. Scaramanga. I've had just about enough of this. Just stop leaning on me. You go around waving that damned gun of yours and acting like God Almighty'"	<b>Grandiose sense of self-worth</b>
"Knowing that he was going to kill Bond later that day Scaramanga said to Bond: 'All right, my friend. Now then, you get up front with the driver'"	<b>Superficial charm</b>
"Of course. He [Bond] was fighting for his life. The other man [Scaramanga] was just amusing himself - providing sport for his friends, displaying his potency, showing off"	<b>Callousness/lack of empathy</b>
"[Scaramanga:] 'I eat one of their famous secret agents for breakfast from time to time. Only ten days ago, I disposed of one of them who came nosing after me'"	<b>Lack of remorse or guilt</b>

Abbreviation. PCL-R: Psychopathy Checklist-Revised

## Discussion

The scientific/medical literature on Ian Fleming's fictional hero has so far mainly focused on his drinking behaviour<sup>20,21</sup> and promiscuous sex life<sup>22</sup>. Recently, James Bond villains have attracted the attention of medically-informed readers for their poor knowledge of neuroanatomy<sup>23,24</sup>. In our analysis of Fleming's novels, we have identified a number of quotations showing that individual PCL-R criteria are met by the examined James Bond villains (Tab. VIII).

The most commonly observed psychopathic trait is callousness/lack of empathy, which is portrayed by all Bond villains. Fleming's novels are easy to read and relatively short, yet entertaining, which makes them ideal texts for budding clinicians and professionals alike to hone their ability to detect the psychopathic traits in the narratives of service users. Moreover, the portrayed psychopathic traits are often to be found in the monologues of villains, which are comparable to the histories of patients, albeit with a more dramatic and fantastic flavor in the fictional characters. It is unlikely that Ian Fleming set out to portray clinically defined psychopathic personalities in his villains; instead, the fictional characters probably assumed psychopathic traits by dint of their villainy. As a result, James Bond villains cannot be considered perfect examples of real-life psychopathic individuals.

The late Italian writer Umberto Eco pointed out that Fleming's James Bond novels follow a formalistic pattern whereby in each novel the villain plays a key role for the development of the plot<sup>25</sup>. The typical scheme is

as follows: Bond is sent by his boss M to a given place to avert an evil plan by a villain (described as a monstrous individual of uncertain origin). In facing the villain, Bond meets a woman, with whom he establishes a erotic relationship interrupted by capture by the villain and by torture. The villain is invariably defeated by Bond, and dies horribly. Bond himself, after resting from his great efforts in the arms of the woman, is eventually destined to lose her. Contrary to Bond, the villains appear to be monstrous. Physical monstrosity is a constant point among the examined villains, as only Emilio Largo's monstrosity is purely mental. Eco highlighted that there is also a racial quality common to all villains: they tend to be of mixed blood and their origins are complex and obscure. The villains are usually born in an ethnic area that stretches from Central Europe to the Slavic countries and to the Mediterranean basin<sup>25</sup>. The typical characteristics of the villains (cupidity elevated to the dignity of paranoia, satrapic luxury, physical and mental excess, perversion, radical disloyalty) are opposed to the sober qualities of James Bond, resulting in what Eco describes as a Manichean dichotomy of Good and Evil, which is functional to Fleming's narrative apparatus<sup>25</sup>. If M is the King and Bond is the Knight entrusted with a salvific mission, the villain is the Dragon; at the same time, the Lady and the villain stand for Beauty and the Beast, whilst Bond plays the role of the Prince who rescues Sleeping Beauty. More recently, it has been suggested that James Bond and the villains might be more alike than previously thought, as they might in fact share psychopathic

**TABLE VIII.** *Individual psychopathic traits (PCL-R) met by the examined James Bond villains.*

Psychopathic trait	Mr. Big	Dr. No	Goldfinger	Emilio Largo	Blofeld	Scaramanga
Glibness/superficial charm		x	x	x		x
Grandiose sense of self-worth	x	x			x	x
Need for stimulation/proneness to boredom	x				x	
Pathological lying						
Conning/manipulative behaviour		x	x			
Lack of remorse or guilt	x	x		x	x	x
Shallow affect			x			
Callousness/lack of empathy	x	x	x	x	x	x
Failure to accept responsibility for actions					x	
Parasitic lifestyle						
Poor behavioural control						
Promiscuous sexual behaviour	x		x	x		x
Early behaviour problems						
Lack of realistic long-term goals						
Impulsivity						
Irresponsibility						
Juvenile delinquency						x
Parole/probation violations						
Committing a wide variety of crimes	x	x	x	x	x	
Many short-term relationships						

Abbreviation. PCL-R: Psychopathy Checklist-Revised

traits<sup>26,27</sup>. Specifically, the Dark Triad of Machiavellianism, narcissism, and psychopathy has been referred to as 'James Bond psychology'<sup>28</sup>. Although Bond ostensibly operates with the (loose) sanctioning of the British government, he frequently operates outside the law: he has a license to kill and frequently uses his repertoire of manipulative tactics to fulfill his missions. Bond has a killer instinct: his psychological disposition that allows him to kill others with a gun or by hand resembles psychopathic cold, uncaring attitudes toward others and limited empathy that facilitates interpersonal aggression. A scene from 'The man with the golden gun', in which James Bond literally sits down and has dinner with the villain Scaramanga, is particularly telling: the villain tells Bond that he (an assassin) and James Bond are the same. Bond's only objection is that when he kills it is by order of his government and those he kills are killers themselves<sup>29</sup>.

Psychopathy is often used as synonym for other antisocial behavioural conditions e.g. conduct disorder and antisocial personality disorder. However, psychopathy should be distinguished from these conditions as it appears to have a stronger heritability<sup>30</sup>, a distinct neuro-

biology primarily affecting the paralimbic regions of the brain<sup>31</sup>, and a poorer prognosis (specifically, violent recidivism)<sup>32</sup>. Despite potentially having serious forensic consequences<sup>32</sup>, psychopathy is not recognized by the ICD-10<sup>33</sup> or DSM-5<sup>34</sup>. Instead, elements of psychopathy are included in the criteria for antisocial personality disorder, explaining the overlapping between the two conditions. Psychopathic personality traits fall on a continuum from absent to severe<sup>35</sup>. Therefore, doctors are likely to encounter patients with psychopathic traits in all areas, although more often in forensic settings. Considering the risk of violence from psychopathic individuals<sup>32</sup>, it is important to be able to identify psychopathic traits displayed by patients. Using the arts as an educational tool in psychiatry is a burgeoning field, gaining momentum especially in the realms of film<sup>36</sup> and literature<sup>37</sup>. Cinema is recognized as a useful medium for teaching about psychopathy<sup>38</sup>. Similarly, literature may also play a role in educating students on this condition. One of the ways literature may be useful is by enabling the reader to practice, in a relaxed and comfortable setting, interpreting the narrative of a patient's history by interpreting the narrative of a novel<sup>39</sup>.

Although it is difficult to objectively quantify the benefit of literature for psychiatry, there have been suggestions about its educational value in this context. An important caveat is the risk of reinforcing negative and harmful stereotypes about mental illness. A further problem is the lack of direct contact with the examined individual, resulting in excessive reliance on indirect information. These issues have not prevented the publication of remote psychodiagnostics investigations on public figures (especially politicians and artists)<sup>40-43</sup>, as well as fictional characters<sup>44</sup>. In 1973, in the wake of the notorious survey of psychiatrists' opinions about Republican presidential candidate Barry Goldwater's psychological profile, the American Psychiatric Association adopted an ethics annotation that came to be called "Goldwater rule". The Goldwater rule was included as section 7.3 in the American Psychiatric Association's Principles of Medical Ethics, which states that it is unethical for psychiatrists to give a professional opinion about public figures whom they have not examined in person, and from whom they have not obtained consent to discuss their mental health in public statements<sup>45</sup>. Criminal and forensic psychologists and psychiatrists, as well as specialists working for intelligence agencies, are generally held exempt from this rule. Moreover, the Goldwater rule applies only to living persons, not to fictional characters. This leaves teachers and students of psychiatry and psychology, alongside readers in general, the opportunity to practice recognising clinically relevant psychological traits in the large and diverse population of fictional characters<sup>46</sup>.

## Conclusions

After reviewing a sample of Ian Fleming's novels, we found ample evidence of the presence of specific psychopathic traits from the PCL-R in James Bond villains. The most commonly observed psychopathic trait is callousness/lack of empathy, which is portrayed by all the examined characters of villains. Contrary to Bond, the villains are consistently described as having physical monstrosity (with only one exception of purely mental monstrosity), as well as obscure ethnic origin and/or complex genealogy. The villains' psychopathic traits appear to be functional to Fleming's narrative scheme, that revolves around the Bond-villain (Good/Evil) dichotomy. For example, the villains' pathological sense of grandiosity, exemplified by the lavish luxury they surround themselves with, is contrasted with Bond's sober qualities. However it has been suggested that the Bond-villain dichotomy is only partial, as a few psychopathic traits appear to be shared by Bond himself. Despite the difficulties of implementing literature in the curriculum of medical students and psychiatry trainees, in consideration of its potential for benefit, a healthy interest in literature should be encouraged, possibly in the form of book clubs<sup>47</sup>. It is vital that Fleming's James Bond novels – or any art forms that are used as an educational tool – are critically appraised in the context of other, more didactic, learning resources with clear learning objectives set out and adhered to. Finally, specific arrangements should be in place so that the process of extracting clinically useful knowledge from literature does not detract from the intrinsic pleasure of enjoying fiction and art.

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## The use of mechanical restraint in a psychiatric setting: an observational study

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### SUMMARY

#### Objectives

The use of mechanical restraints is a practice used both in hospital and extra-hospital settings. This paper aims to outline the socio-demographic and clinical variables related to physical containment.

#### Methods

This observational study evaluates data from 65 adult psychiatric inpatients hospitalized at General Hospital Psychiatric Ward in Varese, Northern Italy, from January 2016 to August 2017.

#### Results

Patients were found to be mainly males (61.5%), with an average age of 43 years (Tab. I). The main reasons for restraints resulted to be "confusion" (81.5%), followed by "aggression" (61.5%) and "opposition to treatments" (20%). A positive correlation between length of hospitalization and numbers of episodes of restraint was found (Tab. II). Furthermore, a statistically significant correlation between female gender and number of restraints for single hospitalization emerged ( $p = 0.039$ ) (Tab. III). Schizophrenia spectrum disorder was the most represented diagnosis, accounting for 44.60% of the sample (Tab. IV).

#### Conclusions

The study provides an overview on patients' characteristics and variables related to mechanical restraints. An early identification of these factors can be useful in the management of confused and agitated patients in order to reduce the episodes of restraint.

**Key words:** physical restraint, involuntary admission, compulsory admission, coercive measure

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#### Conflict of interest

The Authors declare no conflict of interest

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### Introduction

The use of restraints is a practice used both in hospital and extra-hospital settings, such as emergency medicine, psychiatry, geriatrics and nursing homes<sup>1</sup> and it has always aroused clinical and ethical debates, but only in recent years it has returned to be a topic of scientific discussion<sup>2</sup>. This change is in part due to the greater attention paid to patients' perception of treatment, therapeutic alliance, prevention strategies and early rehabilitation and to patients' coping and resilience factors<sup>3-8</sup>. It is known that physical restraint can represent a trauma for patients, determining a worse therapeutic alliance and a worse outcome<sup>9</sup> and that relational methods to prevent and control aggressive behavior and agitation are the first-lines strategies<sup>10</sup>. Even so an increasing consumption of novel psychoactive substances, such as smart drugs, with unpredictable effects, has led to an increasing utilization of emergency care, physical restraint and psychiatric consultation<sup>11-12</sup>. Moreover in some cases, such as in the drug addicts and

malingers, agitation and aggression can be feigned in order to obtain drugs or secondary advantages<sup>13-15</sup>. Other frequent causes of agitation and aggressive behavior, little responsive to relational containment, are related to organic factors that can lead to cognition's alterations: brain trauma, dementia, mental confusion induced by organic and metabolic causes, pain, infections and medications<sup>16-20</sup>. Among psychiatric disorders, as shown by literature, schizophrenia, bipolar disorder and personality disorders<sup>21</sup> are more frequently associated with aggressive behavior and agitation.

There are different kinds of coercive strategies: a) pharmacological restraint: the use of medications in order to obtain sedation; b) environmental restraint: limitation of personal freedom to access all areas of the environment; c) mechanical restraint: any mechanical device that immobilizes or reduces patient's ability to move<sup>22-23</sup>. As far as pharmacological containment is concerned, the molecules used are generally chosen basing on the diagnoses, respiratory, cardiac and metabolic comorbidities as well as individual tolerability, and in elderly or compromised patients on an organic level, although pharmacological restraint does not always appear to be an applicable strategy<sup>24-25</sup>. Regarding environmental restraint, if isolation can prevent aggression, on the other hand can predispose to aggressive behaviour<sup>26-27</sup>. In some situations, such as psychotropic substances abuse, mechanical restraints can be considered safer than drug containment, because of possible adverse reactions; on the other hand, mechanical restraint can be associated with a higher risk of thromboembolic events, respiratory distress and trauma<sup>28</sup>. Moreover, this experience is often lived by the patient with enormous suffering, with the development of traumatic memories and with the onset of post-traumatic stress disorder (PTSD) as well as in many cases with the risk of reinforce aggression<sup>29</sup>. For these reasons, the European Committee for the Prevention of Torture and Inhuman or Degrading Treatment of Punishment considers mechanical restraint an issue of particular concern, justifying it only very rarely<sup>30</sup>. In light of these considerations, the early identification of risk factors associated with aggression and violence could prevent the need for physical restraint. The characteristics of patients who are more frequently subjected to mechanical restraint measures in the psychiatric environment are still uncertain and not well defined<sup>31-32</sup>.

This paper aims to outline the socio-demographic and clinical features related to physical containment in a sample of patients admitted to the Psychiatric Ward.

## Materials and methods

This observational study was conducted in the psychiatric ward of "Azienda Socio Sanitaria Territoriale dei

Sette Laghi – Varese", a teaching hospital in Northern Italy (Deliberate n. VIII/4221, February 28th, 2007). Data from 65 adult psychiatric inpatients hospitalized at General Hospital Psychiatric Ward (SPDC) in Varese from January 2016 to August 2017 were collected. All patients included in the study had to be  $\geq 18$  years old. To avoid duplication, we included only data referring to first hospitalization of the recruitment period of patients who had multiple admissions. The following clinical data have been taken into consideration: period of hospitalization; diagnosis; number of restraints and total length of them during a single admission; substance abuse; hospitalization regime (compulsory or voluntary); previous hospitalizations (distinguishing between compulsory or voluntary), reason for restraint. In order to examine the causes of restraints, the reasons for containment, reported in the medical record and in the nursing register, were grouped in 4 categories: "confusion"; "aggression"; "opposition to therapies"; "other". The restraint time was considered as the sum of all the restraints that occurred during the hospitalization. Data collection was integrated into the normal diagnostic assessment procedure and quality check processes. Data were obtained by consulting:

- restraints' records for the years 2016-2017: including all cases of restraint (start and end times, length, presence of law enforcement, reason for restraint, type of admission, signature of the prescribing doctor and the nurse in charge);
- management software "Portale": information on patients' age, sex, nationality, outpatient service to which patients refer at discharge, beginning and end of hospitalization in which a restraint episode was detected, primary and secondary diagnosis, substance abuse, previous voluntary and/or compulsory admission, home therapy, discharge therapy and contacts for treatment continuation;
- medical records: containing the patient's personal and clinical information relating to the period of hospitalization.

Clinical discharge diagnosis was recorded using the International Classification of Diseases, 11<sup>th</sup> edition (ICD-11). Since the study is a descriptive observational investigation, an informed consent was not required. Data were analyzed anonymously. All personally sensitive information contained in the database used for this study was previously de-identified according to the Italian legislation (D.L. 196/2003, art. 110, -24 July 2008 art. 13). The study was carried out in accordance with the Declaration of Helsinki (with amendments) and Good Clinical Practice. Statistical analysis was performed by IBM SPSS Statistics version 25.0. For descriptions of socio-demographic and clinical variables, a descriptive statistical analysis was performed, while the bivariate

correlation was used to correlate sociodemographic and clinical characteristics to the restraining episodes. All statistical tests were two-tailed, with  $p < 0.05$  considered statistically significant.

## Results

Table I reports patients' socio-demographic and clinical data (Tab. I). The comparison between age and sex shows that in the juvenile age groups mechanical restraints prevail in male patients, while in the most advanced age groups this trend appears reversed. The population is divided between the two possible hospitalization modalities: 48% of patients were compulsorily admitted, while 52% were voluntarily hospitalized. Dating back to the year 2000, 61.5% of patients have had at least a previous admission; 27.7% have had a previous compulsory admission. The average length of hospitalization was 21 days, with s of 13 days, (range from 2 to 153); the length of hospitalization appears to be greater in males, without a difference statistically significant between genders. The bivariate correlation

between length of hospitalization and numbers of episodes of restraints appears to be statistically significant, as shown in Table II ( $p = 0.0004$ ).

The average number of containment episodes per subject was 3.3, while the median was 1, (range 1-41). 54% of patients had only one coercive act during the hospitalization, while 8% of patients were contained more than 10 times. The 25% of the patients examined have a history of substance abuse; cannabinoids, cocaine and alcohol were the most consumed substances. However, substance abuse was not significantly related to restraint, as found with Pearson's correlation. Despite the fact that male patients are contained more frequently than women, a statistically significant correlation between female gender and number of restraints for single hospitalization emerged ( $p = 0.039$ ); considering a single hospitalization, it appears that almost 61% of the restraint episodes are carried out on female patients, as shown in Table III.

The average restraint time, considering as the sum of all the episodes occurred during the hospitalization, was

**TABLE I.** *Socio-demographic and clinical features.*

Gender		Nationality		Previous psychiatric contacts		Type of admission		Substance use	
Male	Female	Italian	Foreign	Yes	Not	Compulsory	Voluntary	Yes	Not
61%	39%	88%	12%	77%	23%	48%	52%	25%	75%
N = 40	N = 25	N = 57	N = 8	N = 50	N = 15	N = 31	N = 34	N = 16	N = 49

**TABLE II.** *Correlation between number of restraints and length of hospitalization.*

		Number of restraints	Length of hospitalization
Number of restraints	Pearson's correlation	1	.518
	Sig. (2-code)		.000
	N	62	61
Length of hospitalization	Pearson's correlation	.518	1
	Sig. (2-code)	.000	
	N	61	61

**TABLE III.** *Correlation between gender and number of restraints.*

		Sex	Number of restraints
Sex	Pearson's correlation	1	.263
	Sig. (2-code)		.039
	N	63	62
Number of restraints	Pearson's correlation	.263	1
	Sig. (2-code)	.039	
	N	62	62

**TABLE IV.** Sample distribution according to diagnosis.

Diagnosis	%
Schizophrenia, schizotypal disorder and delusional disorders	(N = 29) 44.60%
Mood disorders	(N = 17) 26.30%
Behavioral syndromes associated with physiological dysfunctions and physical factors	(N = 2) 3.10%
Personality and behavioral disorders in adults	(N = 14) 21.50%
Intellectual disability	(N = 1) 1.50%
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	(N = 1) 1.50%
Missing data	(N = 1) 1.50%

54.5 hours, the median was 34 hours. 58.4% of patients had at least one restraint episode lasted more than 24 hours. Total duration of restraints was longer in male patients (average 62 hours) than in female patients (average 42 hours). Table IV shows the distribution of the considered population according to diagnosis. In male patients the most represented diagnosis was schizophrenia (57.5%), while among female patients mood disorders (40%), followed by schizophrenia and personality and behavior disorders (24% for each one).

The main reasons responsible of restraints use resulted to be "confusion" (81.5%), followed by "aggression" (61.5%) and "opposition to treatments" (20%). The bivariate correlation between restraints cause and number of containments during a single hospitalization showed a slightly statistical significance ( $p = 0.0052$ ). Furthermore, a statistically significant correlation between the length of hospitalization and "confusion" as reason of restraint, emerges ( $p = 0.022$ ).

## Discussion

Regarding the relation between sociodemographic variables and restraints, the results of the study appear to be in line with the literature's data. Male patients are more often subject to mechanical restraints<sup>33</sup>. However, it is interesting to note that the greater number of restraints for single hospitalizations resulted among female patients. This could be explained by the type of detected diagnosis; the main diagnosis in male patients resulted schizophrenia, while in women a prevalence of diagnosis of mood disorders (including bipolar disorder type I and II and depression) and personality disorders emerged. Mood disorders and personality disorder are characterized by mood swings and a greater rate of impulsiveness and aggressiveness, leading to an alternation of phases in which patients appear calm and cooperative and phases in which aggression is uncontrolled<sup>34-35</sup>. While the phase of aggression in schizophrenia spectrum disorder, largely supported by the presence of hallucinatory state, generally has a

short duration and a good response to pharmacological containment; moreover in mood disorders and personality disorders it is more common to have fluctuation that make restraints necessary even afterwards a period of good behavioral control<sup>36</sup>. Another interesting datum is the statistically significant linear relationship between the duration of hospitalization and the number of restraints. On one hand, this relationship can be explained from the fact that more severe psychopathologies with clamorous manifestations tend to require long time for remission, on the other hand, several findings in professional literature show that psychical restraint often cause low compliance in patients, as well as longer hospitalizations and a worse quality of life<sup>36</sup>. Observing the reasons that led to the physical containment, mental confusion emerged as the most common cause, differently from the literature where aggression resulted to be the main reason<sup>25,37</sup>. This data is not of unambiguous interpretation. In different countries confused patients are likely to be managed in different departments, such as neurology, geriatrics, medicine, so they are not included in the statistics of psychiatric departments<sup>38</sup>. It is evident that the remission of agitation in confused patients is longer and much less predictable than in pure psychiatric diagnoses<sup>38</sup>. The majority of restraint episodes (75.4%) occurred in patients that do not use psychotropic substances. However, this datum could be underestimated for the increasing diffusion of smart drugs or novel psychoactive substances, which are often not traceable in standard drug tests<sup>39</sup>. These subjects are particularly difficult not only for the diagnostic assessment, but also for the treatment. In fact, those molecules can present interactions with medicaments both counteracting the therapeutic effects and worsening the side effects<sup>39</sup>. The main limitation of this study is that it evaluates only restrained patients, without a control group. Other important study limitations are the lack of an instrument to assess personality disorder diagnosis, based only on clinical observation, the absence of the evaluation of patients' perception or of the onset of

PTSD after restraint use. The estimation of this disturb, that frequently occurs in patients subjected to coercive measures, could represent a future goal of study. Moreover, the recruitment in a single hospital gives few clues about the national and international reality about the restraint's phenomenon. Despite these limitations, the study provides an overview on the characteristics and variables related to mechanical restraint use. An early identification of these factors can be useful in the management of agitation and aggression.

## Conclusions

It is not yet known whether physical restraints can be a factor of worsening the patient's clinical progress and increase the length of hospitalization. In light of the growing attention to recovery style and resilience factors, it is interesting to investigate whether physical restraint can represent an obstacle to an optimal patient recovery and if early modification of possible associated factors to restraints use could limit its recourse.

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# Initial treatment retention for habit reversal training in adults with Tourette syndrome

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## SUMMARY

### Objective

Tourette syndrome (TS) is a chronic neuropsychiatric disorder characterised by multiple motor and phonic tics. Habit Reversal Training (HRT) is increasingly recognised as an effective behavioural intervention in the treatment of tics, however little is known about the characteristics of adult patients who attend HRT sessions.

### Methods

In this study, the demographic and clinical characteristics of 57 adult patients with TS consecutively referred to HRT intervention were retrospectively reviewed. Correlation and regression analyses were used to examine associations between patients' characteristics and their HRT attendance.

### Results

Twelve out of 57 patients were excluded from the analysis because of inappropriate referral and/or insufficient data. One in three of the remaining patients (15/45) failed to attend HRT following referral by the treating consultant. There were no significant differences in the demographic or clinical characteristics between patients who attended HRT and patients who did not. A trend towards statistical significance ( $p = 0.08$ ) was found for decreased tic severity as predictor of poor attendance.

### Conclusions

Our findings suggest that initial treatment retention for HRT in TS can be suboptimal and reasons for poor attendance might be external to demographic or clinical factors. The statistical trend for decreased tic severity as predictor of poor attendance is of potential clinical relevance and needs replication. Further investigations on larger clinical samples will help to optimise care pathways and resource allocation strategies for patients with tics referred to behavioural interventions.

**Key words:** Tourette syndrome, tics, habit reversal training, behaviour, initial treatment retention attendance

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### Conflict of interest

The Authors declare no conflict of interest

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## Introduction

Tourette syndrome (TS) is a chronic neuropsychiatric disorder first described by George Gilles de la Tourette in 1885 and characterised by the concomitant presence of multiple motor tics and one or more phonic (vocal) tics<sup>1</sup>. TS has a worldwide prevalence of 1% in the school age population and typically begins in childhood with a mean onset of 7 years<sup>2</sup>. Tics are defined as a sudden, rapid, recurrent, non-rhythmic, stereotyped movements or vocalisations; their number, frequency, severity and complexity characteristically change over time. Motor and vocal tics are further classified as simple (i.e. involving a single muscle or group of muscles) and complex (i.e. involving co-ordinated movements mimicking normal motor acts). Tics are usually preceded by premonitory urges or

sensory tics, which are described as unpleasant sensations of mounting inner tension relieved on completion of the tic<sup>3-6</sup>. Behavioural co-morbidities, especially obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD), are commonly reported among patients with TS<sup>7-8</sup>.

Current treatment of TS aims to improve social functioning, self-esteem and health-related quality of life<sup>9</sup>. Pharmacological treatment of tics may be considered if daily functioning of the patient is affected. First-line medications are dopamine antagonists or alpha-2 agonists and current research indicates that tics are most effectively suppressed by antipsychotic medications, such as neuroleptics (e.g. haloperidol, pimozide) and atypicals (e.g. risperidone, aripiprazole)<sup>10</sup>. However a considerable proportion of patients refuse or discontinue medication because of unwanted side effects, whilst others fail to respond to conventional pharmacotherapy<sup>11</sup>. These drawbacks have led to renewed interest in behavioural interventions either alone or as an adjunct to pharmacological treatments<sup>12,13</sup>. Behavioural interventions attempt to identify and modify events associated with tic severity, exacerbation and maintenance. Controlled trials support the application of behavioural interventions to effectively reduce tic expression and improve health-related quality of life<sup>13,14</sup>.

Habit Reversal Training (HRT) is a behavioural intervention first developed for repetitive behaviours by Azrin and Nunn in 1973<sup>15</sup>. The primary components of HRT are awareness training and competing response. Awareness training encourages patients to increase their knowledge of their tic behaviour and premonitory urges, in order to facilitate better self-control<sup>16</sup>. Patients are taught a competing response often using antagonist muscles in order to control the target tic by performing an opposing movement<sup>16</sup>. The success of HRT has been exemplified in a number of individual case reports and original studies<sup>17,18</sup>, including a recent large scale randomised controlled trial involving both children<sup>4</sup> and adults<sup>19</sup>. Although there is empirical evidence to demonstrate the use of HRT in TS to effectively decrease tic severity, little is known regarding the characteristics of patients who attend HRT sessions. As highlighted by previous studies, poor attendance and compliance to HRT results in a lack of improvement in tic symptoms<sup>20,21</sup>. In the largest study to date, out of 61 children assigned to receive HRT almost 10% discontinued the intervention and did not complete the study<sup>4</sup>. An earlier randomised controlled trial reported an even higher drop-out rate of 18% in 4 out of 22 adults with TS receiving HRT<sup>14</sup>.

The aim of this retrospective study was to determine the demographic and clinical characteristics of adult patients with TS who attend HRT intervention in order

to develop recommendations for treating clinicians on appropriate referrals. This is important as it could help prevent inappropriate use of resources and therapist appointment times, in addition to increased waiting time for more suitable patients.

## Methods

### Participants

The present study is a retrospective review of data collected from a cohort of adult patients attending the specialist TS clinic at the Department of Neuropsychiatry, BSMHFT and University of Birmingham, United Kingdom. We systematically collected clinical and demographic data from all consecutive patients with a DSM-validated diagnosis of TS who were referred to HRT intervention over a period of 18 months. Patients were excluded from this study if they were below 16 years of age, had limited understanding of English, reading level less than secondary school level, learning disabilities, or significant missing data in their medical records.

### Clinical measures

All patients underwent complete neuropsychiatric evaluation, which included the use of standardised psychometric instruments. The National Hospital Interview Schedule for Tourette syndrome (NHIS-TS), a detailed semi-structured interview schedule for patients with TS, was used to collect demographic and clinical details including family history of TS and co-morbid conditions<sup>22</sup>. Baseline tic severity of each patient was measured using the Yale Global Tic Severity Scale (YGTSS), a clinician-rated instrument designed for use in TS and other tic disorders. In the YGTSS, both motor and vocal tics are rated a score of 0-5 according to number, frequency, intensity, complexity, and interference. These scores are summed to give a score for motor and vocal tics out of 25 and a combined total tic score out of 50. A further 0-50 overall impairment score is added to yield the total YGTSS score, where higher scores indicate greater tic severity<sup>23</sup>. The Diagnostic Confidence Index (DCI) was used to strengthen the clinician's confidence in making a diagnosis of TS by assessing the presence of both simple and complex TS, including coprolalia, copropraxia, echopraxia, echolalia and palilalia. DCI scores range between 0-100, with higher scores indicating higher diagnostic confidence<sup>24</sup>.

Data regarding HRT attendance were collected through the appropriate HRT referral and appointment letters from relevant care-records. Attendance was defined as whether or not the patient made successful contact with the HRT therapist following their initial assessment by the referring clinician. Patients provided informed written consent prior to their participation to this study, for

which ethical approval was obtained from the South Birmingham Research Ethics Committee, Research and Development Department at BSMHFT and the University of Birmingham BMedSc Population Sciences and Humanities Internal Ethics Review Committee.

### Statistical analysis

Statistical analyses were performed using SPSS version 18.0 statistics software. Univariate analyses were carried out to examine whether or not each clinical/demographic characteristic was associated with attendance versus non-attendance. The chi-square test was applied to categorical data and the Mann-Whitney U test was performed on numerical data. The combined effect of potential predictors of the demographic and clinical characteristics on attendance at HRT sessions was examined using stepwise logistic regression.

## Results

Data were collected on 57 patients. Of these, 12 were excluded due to inappropriate referral or incomplete documentation. Statistical analyses were carried out on the remaining 45 patients; of these, 15 (33%) failed to attend at all. The clinical and demographic characteristics of our sample are shown in Table I.

The association between patients' demographic/clinical characteristics and attendance at the treatment sessions was analysed using Student t-test for normally distributed data (YGTSS and DCI; Shapiro-Wilk test of normality:  $p > 0.05$ ) and Mann-Whitney U test for age and duration, which did not show normal distribution (Shapiro-Wilk test of normality:  $p < 0.05$ ). Categorical data (gender, family history, medication, co-morbid ADHD, co-morbid OCD, presence of tic-related symptoms) were analysed using chi-square test. The results of these analyses are shown in Tab. II. There were no differences in either demographic or clinical characteristics between patients who attended the treatment sessions and patients who did not.

All variables were entered into a binary logistic regression model to determine the predictive value of patient demographic/clinical characteristics with respect to attendance at HRT sessions. The results of the logistic regression analyses are presented in Table III. Again, no demographic or clinical characteristic was a significant predictor of attendance at HRT sessions ( $p > 0.05$  for all variables), however we found a trend towards statistical significance ( $p = 0.08$ ) for decreased tic severity as predictor of poor attendance.

## Discussion

The present study aimed to determine the demographic and clinical characteristics of adult patients with TS

**TABLE I.** Demographic and clinical characteristics of the patients with Tourette syndrome referred to Habit Reversal Training ( $n = 45$ ).

Age, years (mean (SD))	29 (11)
<b>Gender (n (%))</b>	
Male	31 (69)
Female	14 (31)
Duration of tics, years (mean (SD))	21 (11)
<b>On medication (n (%))</b>	
Yes	31 (69)
No	14 (31)
<b>Presence of tic-related symptoms (n (%))</b>	
Yes	21 (47)
No	24 (53)
<b>Family history of tics (n (%))</b>	
Yes	21 (47)
No	23 (53)
<b>Presence of co-morbid ADHD (n (%))</b>	
Yes	14 (31)
No	31 (69)
<b>Presence of co-morbid OCD (n (%))</b>	
Yes	16 (36)
No	29 (67)
YGTSS score (mean (SD))	49 (14)
DCI score (mean (SD))	66 (11)

Abbreviations. ADHD: Attention-deficit/hyperactivity disorder; OCD: Obsessive-compulsive disorder; YGTSS: Yale Global Tic Severity Scale; DCI: Diagnostic Confidence Index

who attend HRT intervention. In our clinical sample one in three patients (15/45) failed to attend HRT following referral by the treating consultant, suggesting that initial treatment retention to HRT in TS can be suboptimal. This finding is consistent with the results of a previous randomised controlled trial, which reported a treatment drop-out rate of 18% in 22 adults with TS receiving HRT<sup>14</sup>. The present study also reflects the general knowledge that non-attendance is a common problem in mental health services and high rates of non-attendance are found for different psychological treatments<sup>25-28</sup>.

With regards to possible variables that could predict poor attendance, the results of our study did not show any of the demographic or clinical characteristics examined to be a statistically significant predictor for attendance at HRT sessions. The trend towards statistical significance for decreased tic severity (as measured by YGTSS scores) as predictor of poor attendance is of potential clinical relevance, given the suboptimal treat-

**TABLE II.** Comparison of demographic and clinical characteristics between patients who attended and patients who did not attend Habit Reversal Training.

	Attend (N = 30)	Not attend (N = 15)	Test	P-value
Age, years (mean (SD))	26 (9)	26 (8)	Z = 0.48	0.63
Gender (n (%))			$\chi^2 = 0.52$	0.99
Male	21 (68)	10 (32)		
Female	9 (64)	5 (36)		
Duration of tics, years (mean (SD))	20 (10)	20 (13)	Z = 0.47	0.64
Family history of tics (n (%))			$\chi^2 = 0.40$	0.75
Yes	15 (71)	6 (29)		
No	15 (63)	9 (38)		
Presence of tic-related symptoms (n (%))			$\chi^2 = 0.40$	0.75
Yes	15 (71)	6 (29)		
No	15 (63)	9 (38)		
Medication (n (%))			$\chi^2 = 0.52$	0.99
Yes	21 (68)	10 (32)		
No	9 (64)	5 (36)		
Presence of co-morbid ADHD (n (%))			$\chi^2 = 1.30$	0.32
Yes	11 (79)	3 (21)		
No	19 (61)	12 (39)		
Presence of co-morbid OCD (n (%))			$\chi^2 = 0.19$	0.75
Yes	10 (63)	6 (38)		
No	20 (69)	9 (31)		
YGTSS score (mean (SD))	50.37 (15.01)	44.80 (13.42)	t = 1.21	0.23
DCI score (mean (SD))	66.10 (12.70)	65.80 (8.10)	t = 0.08	0.93

Abbreviations. ADHD: Attention-deficit/hyperactivity disorder; OCD: Obsessive-compulsive disorder; YGTSS: Yale Global Tic Severity Scale; DCI, Diagnostic Confidence Index

**TABLE III.** Results of the logistic regression analysis of the demographic and clinical characteristics as potential predictors of attendance to Habit Reversal Training.

Variable	Attend Odds ratio (95% CI)	P-value
Age	1.03 (0.87 to 1.22)	0.721
Male sex	1.61 (0.30 to 8.68)	0.577
Duration of tics	0.94 (0.80 to 1.11)	0.474
Medication	0.65 (0.10 to 4.32)	0.655
Family history of tics	0.84 (0.16 to 4.61)	0.845
Presence of tic-related symptoms	1.12 (0.23 to 5.41)	0.887
Co-morbid ADHD	3.00 (0.50 to 17.97)	0.230
Co-morbid OCD	0.57 (0.13 to 2.62)	0.472
YGTSS score	1.07 (0.99 to 1.16)	0.080
DCI score	0.96 (0.89 to 1.04)	0.309
Likelihood ratio test $\chi^2$ (df)	13.418 (7), p > 0.05	

Abbreviations. ADHD: Attention-deficit/hyperactivity disorder; OCD: Obsessive-compulsive disorder; YGTSS: Yale Global Tic Severity Scale; DCI: Diagnostic Confidence Index

ment retention. The results of the binary logistic regression analyses suggesting that patients with increased tic severity are more likely to attend HRT sessions following initial referral by the treating consultant can have different explanations. One possible explanation is that patients with a lower tic severity may not feel that their TS affects their quality of life severely enough to justify the amount of time and effort required to attend HRT sessions and engage in the behavioural treatment. At our specialist TS clinic, the basic principles of HRT were routinely introduced and explained by the treating consultant to all consecutive patients with TS without learning and/or linguistic difficulties. Referral to HRT session was solely based on the interest shown by the patient towards commencing the treatment. This may have resulted in a skewed sample of patients, not representative of the whole population of TS patients. The average age of our sample was 29 years and 31 (69%) patients were male. Previous literature has shown that non-attendance at outpatient clinics is significantly associated with being younger and male<sup>29</sup>, therefore a difference between those who attend or not may have been missed due to the low number of female patients. The present study should be considered with respect to limitations. All patients were recruited at a specialist clinic for TS, where more complex clinical presentations are usually referred. This could have introduced referral bias. Given the relatively small sample size, an existing association between the demographic/clinical characteristics and attendance could have been missed. Our study would have been strengthened by collecting data over a longer period of time in order to allow a greater number of patients to be included. Finally, there is a possibility that some potentially relevant variables (e.g. travelling distance to attend the HRT sessions, track record of failure to attend routine appointments) were missed/not included in the present analysis.

Findings from the present study suggest avenues for future research. Firstly, the identified trend towards statistical significance for milder tic severity as predictor of poor attendance prompts further investigation using larger clinical samples. Secondly, data were only collected regarding demographic and clinical characteristics of patients referred to HRT sessions. Previous litera-

ture examining attendance at behavioural interventions has highlighted other factors that may be important predictors of patient attendance at appointments. The findings of the study by Startup et al.<sup>27</sup> suggest that the relationship between patient and therapist is related to engagement with and retention in psychological treatment, reporting drop-outs as less engaged with their therapists: perhaps this could also apply to the relationship with the referring clinician. Furthermore, non-attendance at psychiatric clinics is more likely in patients who have missed previous appointments and those with a long waiting time between referral and appointment<sup>30</sup>. Other patient characteristics that are thought to be associated with poor initial treatment retention include socio-economic class, marital status, family support and employment<sup>31-33</sup>. These factors may be of importance in predicting which patients with TS are more likely to attend HRT sessions and engage in behavioural treatment interventions.

## Conclusions

Non-attendance is an important issue in psychiatry, particularly in the delivery of behavioural interventions, due to the potential waste of health-care resources and therapy appointment times, which might lead to increased waiting times for more suitable patients. Our findings suggest that initial treatment retention to HRT in TS can be suboptimal, with one in three patients (15/45) failing to attend initial appointments following referral by the treating consultant. The trend towards statistical significance for decreased tic severity as predictor of poor attendance is of potential clinical relevance and needs further investigation on larger samples. Future research should also focus on other factors, which may be of importance in predicting the characteristics of patients more likely to attend HRT sessions. With this knowledge, recommendations can be developed for treating clinicians on the delivery of appropriate care pathways in the treatment of TS.

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# Teaching neuroanatomy through a memorable Olympic race

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## SUMMARY

### Objective

The year 2020 marks the 40<sup>th</sup> anniversary of a sporting event that is remembered as one of the greatest comebacks in Olympic sprinting: Pietro Mennea's gold medal in the 200m race at the 1980 Moscow Olympics. Mennea described his own performance as "a great psychological victory, more than physical". In line with Mennea's account, brain surgeon Giulio Maira dedicated a section of his newly published book ('The brain is wider than the sky', 2019) to the activity of Mennea's brain throughout the race, focusing on the activity of 19 key neuroanatomical regions before, during, and after the race.

### Methods

The English adaptation of Maira's text was presented to postgraduate students at the end of a teaching session on neuroanatomy. The 39 occurrences of the 19 key neuroanatomical terms were removed, so that the students were provided with a text format suitable for an educational game. First, the students were introduced to the activity while watching a short videoclip of the thrilling 200 m Olympic final race. Then, the students were asked to fill the gaps in Maira's narration by inserting the missing neuroanatomical terms, based on the contents of the neuroanatomy lecture. One point was assigned for each neuroanatomical term that was correctly identified, with scores ranging from 0 to 39.

### Results

A total of 16 psychiatry trainees actively participated in the educational game, which took about 30 minutes to complete. Student engagement was high, with a wide distribution of scores (mean 14.75; range 5-22). The feedback from the participants was overall positive: the educational value of the game was rated 8.50/10 (range 6-10) on a scale from 1 (lowest value) to 10 (highest value). All students recommended the addition of this activity to the postgraduate training curriculum, and reported that the game increased their interest in neuroanatomy.

### Conclusions

The combination of a short, but memorable, video clip and an original educational game at the end of a neuroanatomy teaching session made the learning experience of psychiatry trainees more engaging and enjoyable. Linking neuroanatomical knowledge to the brain activity of an outstanding athlete, who recognised the role of his mind in his achievements, proved both educational and inspirational.

**Key words:** educational games, neuroanatomy, psychiatry, teaching, training

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## Introduction

The year 2020 marks the 40<sup>th</sup> anniversary of a sporting event that is remembered as one of the greatest comebacks in Olympic sprinting: Pietro Mennea's gold medal in the 200 m race at the 1980 Moscow Olympics<sup>1</sup>. In the 200 m final, Mennea (in lane 8) faced, among others, the third-fastest man in history and reigning champion, Don Quarrie (in lane 4), the fast-

**TABLE I.** Results of the 200 metre final at the 1980 Moscow Olympics.

Athlete	Time
Pietro Mennea	20.19 (gold medal)
Alan Wells	20.21 (silver medal)
Don Quarrie	20.29 (bronze medal)
Silvio Leonard	20.30
Bernhard Hoff	20.50
Leszek Dunecki	20.68
Marian Woronin	20.81
Oswaldo Lara	21.19

est man in the world from 1977, Silvio Leonard (in lane 1), and the newly crowned 100 m champion Allan Wells (in lane 7). Wells got out to a blistering fast start and was ahead of Mennea within the first 50 metres. Coming off the turn, Mennea was at least two metres back, behind all his main competitors, including Wells, Quarrie, and Leonard. Mennea accelerated down the straight, edging closer to them with every step. Towards the end of the straight, Mennea irresistibly gained ground and passed both Quarrie and Leonard. He caught Wells five metres before the finish and continued past him on the finish line, winning the gold by a mere 0.02 seconds. The winner's time was 20.19 (Tab. I).

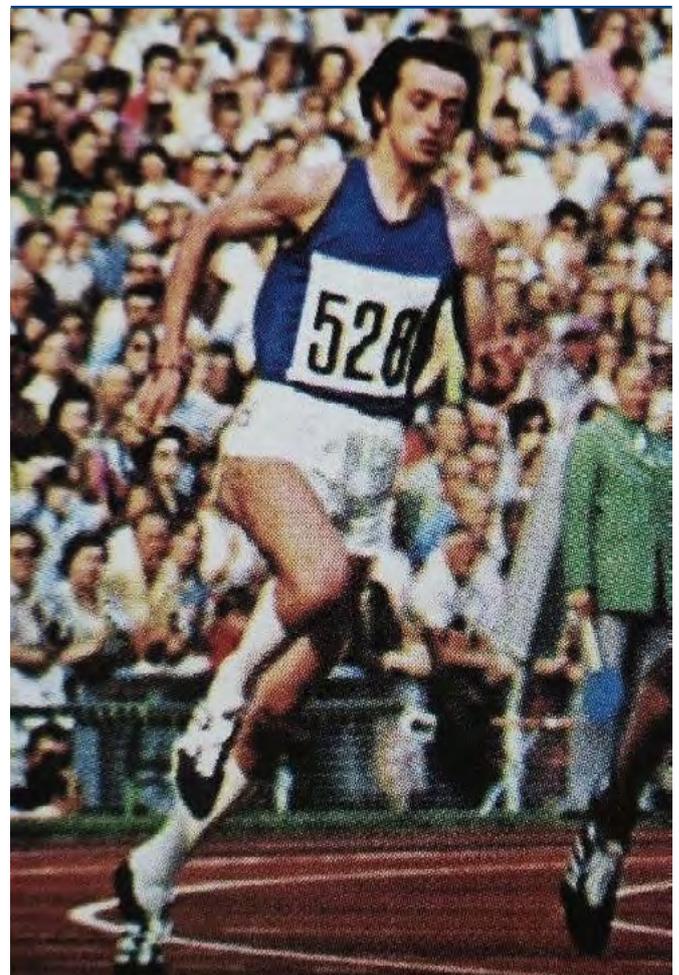
At the time, Mennea (Fig. 1) was the standing world record holder: ten months earlier, in Mexico City, he had run the 200 m in 19.72, a time that stood for almost 17 years as world record (the longest duration in the event history) and is still unbeaten after over 40 years as European record<sup>2,3</sup>. In his exceptionally long career, Mennea competed in a total of five Olympics (1972, 1976, 1980, 1984, 1988), qualifying for the 200 m final in the first four of them – the first track athlete ever to do so. Mennea's accomplishments include academic achievements, as he went on to earn four university degrees: in Political Science, Law, Physical Education, and Literature. In 1997, Asteroid 73891 Pietromennea was named in his honour.

## Methods

Contrary to endurance, comebacks are relatively rare occurrences in sprint running, for several reasons. Performances across top athletes differ by fractions of seconds and winning times do not tend to exceed 10 seconds (in 100 m races) or 20 seconds (in 200 m races). By the time an athlete has been overtaken by a few metres, there is simply no time left for a comeback in the remaining distance within such a short timeframe. There

have been suggestions that Mennea's exceptional brain played a key role in his unexpected 200 m final comeback. Mennea's comments on his performance were as follows: "This is a great psychological victory, more than physical. It had to do with what's inside. Coming down that final stretch, I wanted to win. I wanted it very badly"<sup>4</sup>.

These comments might have been of interest to brain surgeon Giulio Maira, who dedicated a section of his newly published book ('The brain is wider than the sky', 2019) to Mennea's 200 m Olympic race or, more precisely, to the activity of Mennea's brain throughout the race<sup>5</sup>. In four dense pages, Maira details the role purportedly played by the main components of Mennea's brain during the twenty seconds that spanned the athlete's outstanding performance, from when he bent on the starting blocks waiting for the starting signal to the moment he crossed the finish line in first position. In this passage, 19 key neuroanatomical regions are mentioned 39 times in total. Specifically, the motor cortex, the prefrontal cortex, and the visual cortex are

**FIGURE 1.** Pietro Paolo Mennea (1952-2013).

mentioned 5 times each. The amygdala is mentioned 4 times. The cerebellum and the retina are mentioned 3 times each. The hippocampus is mentioned twice. Finally, the auditory cortex, the basal ganglia, the frontal cortex, the limbic system, the nucleus accumbens, the optic nerves, the parietal cortex, the proprioceptive system, the spinal cord, the temporal cortex, the thalamus, and the vestibular system are mentioned once each.

#### *Moscow Olympic stadium, July 28<sup>th</sup> 1980, just after 8 pm*

*An Olympic stadium, a red athletics track, tens of thousands of people screaming with excitement for a show that promises to be thrilling. From their homes, all over the world, millions of people are anxiously waiting in front of their television screens.*

*On the track there are eight men, bent on the blocks, waiting for the start of the race: they will run the 200 m final.*

*In the far right lane, the eight one, there is an athlete wearing a blue shirt. With tension, he looks around at his opponents and, unwillingly, sees in his mind all his previous races, all the months spent training, all the efforts that led him there. His **hippocampus**, the memory centre, is working hard and has a continuous dialogue with the thalamus and with cortical areas to retrieve the memories of many years.*

*His right knee and his hands are on the ground, his eyes forward. In his brain, millions of cells are active: the emotion areas [of the **limbic system**] stimulate the release of adrenaline, the **prefrontal cortex**, the decision-making centre, is ready to activate the cells of the **motor cortex** at the signal to sprint from the blocks. Electrical discharges constantly leave the eyes to convey visual information to the **visual cortex**, while the athlete's gaze continues to shift from the other athletes next to him to the distance that he will have to cover as fast as he can. The photoreceptors located in the **retina** generate a huge number of electrical signals that travel through the **optic nerves** and reach the **thalamus** and the **visual cortex**. From here, the visual information is transferred to the **temporal** and **parietal cortex**, so that what happens on the track is continuously analysed at high speed, and the athlete can activate, when needed, his muscles. The **cerebellum** is ready to coordinate automatic motor patterns stored as procedural memories [in the **basal ganglia**].*

*The **amygdala** is in frantic activity: fear, joy, anxiety, continuous signals to the adrenal gland. The **prefrontal cortex**, the conductor of our brain orchestra, is eager to activate the muscles, but knows that the starting signal will be captured by the **visual** and **auditory cortex**, that will raise the alarm; only then the **prefrontal cortex** will be able to activate the **motor cortex**, as fast as possi-*

*ble, possibly faster than the other athletes. The brain is waiting, ready.*

*At the warning signal, the athlete comes up, his head still down. Finally comes the starting signal. Every component of the brain is now active: as in a giant pinball machine, millions of contacts suddenly light up. These are all the nervous centres that need to be activated so that the running skills can be expressed at their best. The **frontal cortex** receives the auditory signal and plans the starting action, withholding its inhibition over the **motor cortex**. Finally, electrical signals travel down the **spinal cord** to activate the muscles. The **cerebellum** activates to control the coordination of the body movements.*

*As soon as the athlete hears the starting signal, he springs to his feet, stretches his body and starts to run, as always with a delay of a few hundredths of a second compared to the other athletes. He runs in the eight lane, in the most advanced position at the start, apparently ahead of the others. The Scottish athlete in the seventh lane is faster at the start and quickly overtakes him. The **retina**, with its cells that peer into the left hemifield, captures the position of the opponents and sends the information to the **occipital visual cortex**, which processes the retinal images and sends constant messages to the **amygdala**, so that it generates an alarm signal and triggers the release of more adrenaline, as if it were fuel for the engine. Otherwise, the race is lost.*

*The athletes get closer to the bend. The **visual areas**, the **vestibular system**, and the **proprioceptive system** that monitor position, movement, and body posture, register the need to change the race set up. The coordination centres, in the **cerebellum**, signal to the muscles to make the appropriate adjustments: thousands of small corrections are implemented so that the body can maintain its balance. At the end of the bend the brain realises that the other athletes are ahead. On reaching the straight, the athlete is virtually next to last, two-three meters behind the Scottish athlete in the seventh lane who is leading the race.*

*The **amygdala** requires an even more intense effort. The neurotransmitters activate the synapses with increasingly higher frequency so that the legs can increase the pace of their strides. The athlete begins an extraordinary comeback and – in the words of Gianni Brera – ‘the ground seems to flee beneath him’.*

*The finish line is getting closer. In the final meters the mind, lacking oxygen, begins to struggle. The brain tells the heart: ‘More blood’. ‘I can’t give you more than this’, replies the heart to the brain, ‘now it’s up to you: you must resist and make it’. ‘I’ll try’, the brain promises. The **prefrontal cortex** knows that the body will have to reach the limits of human capabilities to win, to push beyond what a man and an athlete can do.*

The **motor cortex** sends continuous impulses to the motor neurons in the spinal cord, so that the muscles activate even more. There is only one man ahead, but the effort is not over: he has to be overtaken. More adrenaline, more discharges of impulses across the brain. While the athlete in blue throws himself onto the finish line, the **retina** takes a final snapshot of the opponents' positions. The **amygdala** explodes with joy as it realizes that now there is no one ahead. With an instinctive movement, the **motor cortex** that controls the movements of the arms activate, and the athlete raises his head and arms towards the sky, pointing above with his index finger. The finish line has been crossed. Dopamine is released, the **nucleus accumbens** (the centre of pleasure) activates, the **hippocampus** stores this moment among the most precious memories, the **prefrontal cortex** signals that the race is over: it's fine to stop now. Pietro Mennea has won. His brain is Olympic champion.

This English adaptation of Maira's text (with minor adjustments) was presented to postgraduate students at the end of a teaching session on neuroanatomy. The 39 occurrences of key neuroanatomical terms (in bold) were removed, so that the students were provided with a text format suitable for a quiz game<sup>6</sup>. First, the students were introduced to the activity while watching a short videoclip (about two minutes, including a slow motion replay) of the thrilling 200 m Olympic final race<sup>7</sup>. Then, the students were asked to fill the gaps in Maira's narration by inserting the missing neuroanatomical terms, based on the contents of the neuroanatomy lecture. One point was assigned for each neuroanatomical term that was correctly identified (with its name or equivalent – e.g. visual cortex and visual area), with a total maximum score of 39.

## Results

The neuroanatomy quiz game based on Maira's report of Mennea's brain activity during his most celebrated race was piloted during a teaching session that was part of the United Kingdom Royal College of Psychiatrists – Core Training scheme. A total of 16 psychiatry trainees actively participated in the quiz game. The educational activity took about 30 minutes to complete. Student engagement was high, with a wide distribution of scores (mean 14.75; range 5-22). The feedback from the participants was overall positive<sup>6</sup>. The educational value of the game was rated 8.50/10 (range 6-10) on a scale from 1 (lowest value) to 10 (highest value). All students recommended the addition of this activity to the curriculum, and reported that the game increased their interest in neuroanatomy. To the question “how likely are you to integrate this activity into your study

habits?” (1, very unlikely; 10, highly likely), the average score was 6.44/10 (range 1-10). To the question “how well does this activity help you to prepare for the exam?” (1, not at all; 10, extremely well), the average score was 7.38/10 (range 5-10). The formative feedback (free text) focused on the suggestion to dedicate more time to this educational activity.

## Discussion

Educational games are immersive active learning strategies, which encourage student interaction and increase the time spent ‘on task’<sup>8,9</sup>. Moreover, quiz games also provide a ‘safe to fail’ environment and immediate feedback to the learner<sup>10-12</sup>. By encouraging students to perform at their individual maximum skill level, immediate feedback promotes engagement with the educational material in a different way and decreases the level of faculty member facilitation involved in the learning exercise<sup>10</sup>. The combination of a short, but memorable, video clip and an original quiz game at the end of a neuroanatomy teaching session made the students' learning experience more engaging and enjoyable<sup>13</sup>. Finally, there was something more to this teaching session. Mennea's life is inspiring more to say the least. His attitude and commitment to training are a testament to meritocracy, in any field. Mennea explained that “the Olympic gold medal was the fruit of years of hard work [...] Talent is not enough to become a world or Olympic champion, you need other qualities [...] During my career, I always trained very hard without trying to take the short route to success [...] I always trained with a lot of passion and determination and my ambition to succeed has pushed me to the highest results in my sport”<sup>14</sup>. Mennea's legacy is summed up in the words of his last television interview: “My sport history has a deep meaning, because I was not a predestined and I built it through my work. I trained for 5-6 hours per day, every day, including Christmas and New Year's Eve, for almost 20 years. This is how I succeeded where many others have failed”<sup>15</sup>. To the question “If you could go back, would you do the same thing?”, Mennea replied “No: instead of 5-6 hours, I would train 8 hours per day – or even more, because that's the secret”<sup>16</sup>. It is therefore not surprising that when Mennea's coach, Carlo Vittori, shared his training schedule at an international meeting, someone commented: “But the person who completed this training is still alive!?!”<sup>17</sup>. Mennea was not exceptionally gifted in his physical structure compared to elite sprinters<sup>18,19</sup>: his height was 1.80 m (5 ft 11 in) and his weight 73 kg (161 lb). However, he understood that his brain could drive him to exceptional results, and his willpower proved it. Sharing his attitude and a few anecdotes about him with the students complements a learning experience that is at once educational and motivational.

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# Off-label prescription of psychotropic medications in a sample of Italian psychiatrists working in private practice: a cross sectional study

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## SUMMARY

### Background

Off-label prescription refers to the use of a drug outside the terms of its Marketing Authorization. According to the literature, this practice is particularly common in clinical psychiatry.

### Objective

To describe patterns of off-label prescription in a sample of Italian psychiatrists working in private practice.

### Methods

An ad hoc questionnaire was developed and sent by e-mail to a sample of Italian psychiatrists working in private practice in the Region Emilia-Romagna. The questionnaire assessed frequency of off-label prescription, reasons associated with it, diagnostic categories more often associated with such practice, main sources of information used to support off-label prescription, and psychotropic agents most commonly prescribed off-label, as well as medical-legal implications. Data were analysed by means of univariate and multivariate ordered logistic regressions.

### Results

Fifty psychiatrists (female: 44%) out of 129 who received the e-mail invitation responded (response rate: 39%). Off-label prescription was found to be inversely proportional to clinicians' age ( $OR = 10.53$  [95% CI 2.13-52.13]). Most commonly, second-generation antipsychotics (SGAs) were prescribed to patients diagnosed with personality disorders (PDs) ( $OR = 0.08$  [95% CI 0.02-0.36]). A higher rate of off-label prescription was also associated to relying more on pharmaceutical sales representatives ( $OR = 0.58$  [95% CI 0.01-0.30]) or personal professionals' clinical experience ( $OR = 0.05$  [95% CI 0.01-0.36]) and less on other colleagues' experience ( $OR = 11.80$  [95% CI 4.16-33.50]) as source of information.

### Conclusions

Off-label prescription is common, especially among young psychiatrists, who frequently rely on previous personal clinical experience, especially when prescribing SGAs for treating patients with PDs. Respondents pointed to the need for further research and training on the topic addressed by the present study.

**Key words:** web survey, off-label prescription, psychiatry, private practice, psychotropic medications.

## Introduction

Off-label prescription is defined as the use in clinical practice of drugs already licensed by the competent regulatory institutions, though outside

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the restricted terms of their market authorization<sup>1</sup>. Four main types of off-label prescription are recognized, depending on whether a drug is used for a different indication, a different group of patients, a different dosage, or a different therapeutic duration than the one approved<sup>2</sup>. Off-label prescription is a widespread phenomenon in various fields of medicine, especially in oncology, anaesthesia, neurology, general medicine, paediatric and child neuropsychiatry<sup>3-7</sup>.

In psychiatry, knowledge on the extent of the phenomenon is very limited, though existing literature supports its wide diffusion in different sub-fields (e.g., adult psychiatry, child and adolescent psychiatry, geriatric psychiatry)<sup>2</sup>. A few reasons were hypothesized as explanations, some common to other medical disciplines, other more specific of psychiatry: first, the lack of licensed medications for many of the diagnostic categories described in the DSM<sup>8</sup>; second, the low rate of clinical effectiveness of licensed therapeutic approaches; third, the need to avoid side effects due to comorbidities<sup>2</sup>; fourth, limited knowledge on the pathogenesis of psychiatric disorders and on specific pharmacological targets<sup>9</sup>. Such reasons may lead psychiatrists to use psychotropic medication for unauthorized indications, or dosages, or to establish complex poly-pharmacotherapies<sup>10</sup>. During 2000-2001 Barbui et al. reported that nearly 50% of SGAs were dispensed off-label<sup>11</sup>, having a more limited range of indications than first-generation antipsychotics (FGAs) and a generally more tolerable profile of side-effects. Aguglia and Salvi (2019) also estimated that nearly 50% of Italian psychiatrists prescribe SGAs off-label very often or often, particularly in case of severe PDs<sup>12</sup>. The very limited changes to the molecular targets of psychotropics since their pre-1960 prototypes, the overall poor knowledge on the mechanisms of action of not only SGAs but also Antidepressants (ADs) and “third-generation” drugs like aripiprazole or cariprazine, combined with the low impact of psychotropics on disabling symptoms such as negative or cognitive symptoms of schizophrenia have resulted in a further increase of off-label or “near-label” prescriptions in the field of mental health<sup>13-16</sup>, particularly when few effective treatments are available<sup>17</sup>.

As elsewhere in the world, in Italy off-label prescription is strictly regulated, with the aim to safeguard the health of patients and to prevent waste of resources<sup>1</sup>. Specifically, three conditions must be satisfied: 1. the patient cannot be treated effectively with any on-label medication; 2. the patient must provide an informed consent; 3. the prescription must be supported by scientific evidence<sup>2,18-20</sup>.

Aim of this study was to assess patterns of off-label prescriptions in a sample of psychiatrists working in their private practice in the Emilia-Romagna Region (Italy),

highlighting frequency and features of prescriptions, and further investigating general knowledge and opinions of clinicians as well as some medico-legal implications of the topic. Our initial assumption was that the practice of off-label prescription would have been found to be very common in this sample.

## Materials and method

### Study design, development and delivery of the research questionnaire

This was a cross-sectional study, carried out by means of an *ad hoc* questionnaire.

A search of relevant scientific literature published on Medline and Scopus since 2000 was initially performed. Further information was derived from the database of the Italian Drug Association (Agenzia italiana del Farmaco, AIFA), specifically guidelines and technical information concerning specific classes of medications.

The most relevant topics were then selected to be addressed by the questionnaire, up to a final choice of 15 items. The questionnaire was developed using the “Online Survey” platform, available on the website [www.sondaggio-online.com](http://www.sondaggio-online.com). Most of the questions were multiple-choice, only one was open-ended and the last two questions were yes/no items. None of the questions were mandatory.

After sociodemographic information (gender, age, years of clinical practice), prescription habits related to off-label use were investigated, consisting of: [a] frequency rate, [b] types and motivations [c], respect of ethical and institutional regulations. Finally, based on results of literature search, a list of the most frequent matches between certain types of psychotropic medications and their off-label use in psychiatric disorders was provided (e.g. olanzapine for anorexia nervosa, or SGAs for PDs) and respondents were asked to mark the matches they used ‘frequently’ in out-patient care. The questionnaire is available upon request to the corresponding author.

The questionnaire was sent to the e-mail contacts of psychiatrists working as private practitioners in the Emilia-Romagna Region (Italy). Names and contacts were searched online referring to the different provinces of the Region, using the keyword “psychiatrist” and after double-checking the professional profiles. A final selection of 129 contacts was obtained and three subsequent rounds of invitations were made between 1<sup>st</sup> April 2018 and 31<sup>st</sup> May 2018.

### Ethical issues

Given the study design, the topic and the population investigated, and after discussing this with referents of the local ethical committee, institutional review board approval was considered unnecessary. Results were

anonymous and sending e-mail addresses were untraceable. Acceptance to fill-in the questionnaire by respondents included consent to analysis and public distribution of results.

### Statistical analysis

Descriptive analysis was carried out using means, medians, frequencies, standard deviations and ranges. Inferential analysis was carried out by ordered logistic regression models, using HAC standard errors. Univariate regressions were initially run, assessing the association of each co-variable with dependent variables, i.e. answer to item 5 of the questionnaire, the frequency of off-label prescription. All co-variables that reached a p-value < 0.25 (to reduce type-II error) were then included in the multiple regression analysis. Finally, the usual level of significance was used ( $p < 0.05$ ) to identify significant associations. The software Gretl was used for the analysis.

## Results

### Description of the sample

Of the 129 psychiatrists working in the Emilia-Romagna Region invited to take part to the study, 50 responded to the survey (response rate: 39%). Since the structure of the online questionnaire allowed respondents to skip questions leaving them unanswered, not every question received 50 answers.

The 44% of respondents were females ( $n = 22$ ). Mean age was  $50 \pm 11$  years and median age was 54 years (range: 32-72 years). Respondents had a mean number of years of clinical practice after specialization of  $20 \pm 11$  years, and a median of 24 years (range: 1-42 years).

The 26% of respondents declared to prescribe off-label psychotropics “often”, 38% “sometimes”, 22% “seldom” and 6% “never”. Four participants (2.0%) of the sample did not answer to this question. Further details are included in Table I.

**TABLE I.** Frequency and reasons for off-label prescription.

Frequency of off-label-prescription	Respondents	Younger*	Older*	Women	Men
Never	3(6.0)	2(66.7)	1(33.3)	1(33.3)	2(66.7)
Seldom	11(22.0)	5(45.5)	6(54.5)	4(36.4)	7(63.6)
Sometimes	19(38.0)	8(42.1)	11(57.9)	10(52.6)	9(47.4)
Often	13(26.0)	10(76.9)	3 (23.1)	5(38.5)	8(61.55)
<b>Motivations for off-label prescription</b>					
Ineffectiveness of previous medication	36(72.0)	18(50.0)	18(50.0)	16(44.4)	20(55.6)
Unavailable on-label medication	20(40.0)	13(65.0)	7(35.0)	6(30.0)	14(70.0)
Medical risk with on-label medication	13(26.0)	5(38.5)	8(61.5)	9(69.2)	4(30.8)
Previous effective off-label medication	11(22.0)	7(63.6)	4(36.4)	5(45.5)	6(54.5)
Side effects of on-going medication	7(14.0)	2(28.6)	5(71.4)	2(28.6)	5(71.4)
<b>Reason to avoid off-label prescription</b>					
Fear of possible side effects	12(24.0)	4 (33.3)	8(66.7)	6(50.0)	6(50.0)
Fear of medical-legal consequences	22(44.0)	12(54.5)	10(45.5)	8(36.4)	14(63.6)
Lack of reliable data on effectiveness	22(44.0)	8(36.4)	14(63.6)	10(45.5)	12(54.5)
<b>Off-label use in DSM 5 categories</b>					
Personality Disorders	35(70.0)	20(57.1)	15(42.9)	18(51.4)	17(48.6)
Neurocognitive Disorder	15(30.0)	6(40.0)	9(60.0)	9(60.0)	6(40.0)
Sleep disorders	14(28.0)	6(42.9)	8(57.1)	7(50.0)	7(50.0)
Obsessive-Compulsive Disorder	11(22.0)	7(63.6)	4(36.4)	4(36.4)	7(63.6)
Major Depressive Disorder	11(22.0)	6(54.5)	5(45.5)	3(27.3)	8(72.7)
Eating Behaviour Disorders	11(22.0)	4(36.4)	7(63.6)	5(45.5)	6(54.5)
Intellectual Disability	10(20.0)	6(60.0)	4(40.0)	5(50.0)	5(50.0)
Bipolar disorder	6(12.0)	4(66.7)	2(33.3)	2(33.3)	4(66.7)
Anxiety disorder	5(10.0)	1(20.0)	4(80.0)	1(20.0)	4(80.0)



TABLE I. *continue*

Off-label use in DSM 5 categories	Respondents	Younger*	Older*	Women	Men
Schizophrenia spectrum disorders	4(8.0)	2(50)	2(50)	0(0.0)	4(100.0)
Autism spectrum disorder	3(6.0)	2(66.7)	1(33.3)	1(33.3)	2(66.7)
<b>Subsequent specific clinical actions</b>					
Written informed consent	18(36.0)	10(55.6)	8(44.4)	9(50.0)	9(50.0)
Oral informed consent	24(48.0)	11(45.8)	13(54.2)	10(41.7)	14(58.3)
Increased frequency of visits and exams	14(28.0)	5(35.7)	9(64.3)	9(64.3)	5(35.7)
Update medical records	18(36.0)	12(66.7)	6(33.3)	8(44.4)	10(55.6)
None	3(6.0)				
<b>Sources of information</b>					
Personal clinical experience	31(62.0)	15(48.4)	16(51.6)	14(45.2)	17(54.8)
PubMed	26(52.0)	18(69.2)	8(30.8)	11(42.3)	15(57.7)
Psychiatric scientific literature	25(50.0)	13(52.0)	12(48.0)	10(40.0)	15(60.0)
Clinical experience by colleagues	22(44.0)	12(54.5)	10(45.5)	13(59.1)	9(40.9)
Scientific events	21(42.0)	12(57.1)	9(42.9)	10(17.6)	11(52.4)
Institutional websites	9(18.0)	3(33.3)	6(66.7)	8(88.9)	1(11.1)
Pharmaceutical representatives	7(14.0)	4(57.1)	3(42.9)	4(57.1)	3(42.9)
<b>Most common matches medication/disorder</b>					
SGAs – PDs	34(68.0)	20(58.8)	14(41.2)	14(41.2)	20(58.8)
Mood stabilizers – PDs	32(64.0)	19(59.4)	13(40.6)	12(42.9)	16(57.1)
SSRIs – PDs	34(68.0)	14(41.1)	20(58.8)	5(33.3)	10(66.7)
SGAs – NCDs	27(54.0)	16(59.3)	11(40.7)	11(40.7)	16(59.3)
Trazodone – sleep disturbance	25(50.0)	12(48.0)	13(52.0)	13(52.0)	12(48.0)
Mirtazapine – sleep disturbance	20(40.0)	12(60.0)	8(40.0)	7(35.0)	13(65.0)
Quetiapine – sleep disturbance	18(36.0)	10(55.6)	8(44.4)	7(38.9)	11(61.1)
SGAs – OCDs	23(46.0)	13(56.5)	10(43.5)	6(26.1)	17(73.9)
SSRIs – EBDs	15(30.0)	5(33.3)	10(66.7)	5(33.3)	10(66.7)
Olanzapine – EBDs	5(10.0)	0(0.0)	5(100.0)	2(40.0)	3(60.0)
Quetiapine – GADs	15(30.0)	8(57.1)	6(42.9)	5(35.7)	9(64.3)
Gabapentin – bipolar disorders	9(18.0)	5(55.6)	4(44.4)	5(55.6)	4(44.4)
Trazodone – GADs	9(18.0)	4(44.4)	5(55.6)	5(55.6)	4(44.4)
Valproate – NCDs	4(8.0)	3(75.0)	1(25.0)	0(0.0)	4(100.0)
Paliperidone LAI – schizoaffective disorders	4(8.0)	3(75.0)	1(25.0)	1(25.0)	3(75.0)
Lithium – suicidal behaviours	12(24.0)	9(75.0)	3(25.0)	3(25.0)	9(75.0)

Data expressed as absolute number (percentage).

\*Young(er) psychiatrist  $\leq 54$  years old vs old(er) psychiatrist  $> 54$  years old (based on median value of 54 years in the distribution of age of respondents); SSRIs, selective serotonin reuptake inhibitors; PDs, personality disorders; OCDs, obsessive compulsive disorders; EBDs, eating behaviour disorders; GADs, general anxiety disorders; LAI, long-acting injection; Age, personal clinical experience, pharmaceutical representatives and SGAs – PDs were  $p < 0.25$  at univariate logistic regression.

The most common reason for off-label prescription was ineffectiveness of previous therapies (72%) or unavailability of on-label medications for specific psychiatric disorders (40%). Reasons against off-label prescription were instead

the fear of side effects (24%) or of legal consequences (44%) or the lack of reliable data on effectiveness (44%). The respondents reported more frequent off-label prescriptions when dealing with the following psychiatric

disorders: PDs (70%), Neurocognitive Disorders (NCDs 30%), sleep disorders (28%), Obsessive Compulsive Disorders (OCDs 22%), Major Depressive Disorder (MDD 22%), Eating Behaviour Disorders (EBDs 22%), Intellectual Disability (ID, 20%) and Bipolar Disorder (BP, 12%).

All respondents confirmed that they collect their patients' informed consent when prescribing off-label, but only in the 36% of cases in a written form.

The most common sources of information supporting off-label prescriptions were personal previous clinical experience (62%), PubMed (52%) and other sources of scientific literature (50%).

The most common matches between off-label medications and psychiatric disorders were the following: SGAs, mood stabilizers and SSRIs and PDs (68, 64 and 68% respectively); trazodone, mirtazapine and quetiapine for sleep disturbances (50, 40 and 36% respectively); and SGAs for NCDs (54%).

The majority of respondents deemed the topic of the survey relevant (96%), reporting (60%) that they would like to receive more information on it; respondents rated the questionnaire as being clear and easy to fill in (90 and 96%, respectively).

### Inferential statistical analysis

Table II displays the results of the multivariate regression. The propensity toward off-label prescription was found to be inversely proportional to the age of respondents; moreover, it was associated with a prescription of SGAs in the treatment of PDs and to a higher propensity to rely on personal clinical experience or on information received by pharmaceutical representatives.

## Discussion

Aim of the present study was to analyse the phenomenon of off-label prescription of psychotropic medications in a sample of Italian psychiatrists working in private settings.

The majority of the sample confirmed resorting to off-label prescription "often" and "sometimes", consistently with available literature <sup>21-24</sup>.

The two most common reasons for starting an off-label medication were partial or total ineffectiveness of previous on-label therapeutic actions (72%), or absence of on-label medications for a specific psychiatric disorder (40%). The only partial response to licensed medications of many psychiatric disorders is well documented in international scientific literature: over 20-30% of patients with schizophrenia are resistant to antipsychotics (clozapine included) <sup>25</sup>, more than 40% of people affected by OCDs are resistant to first-line treatments with SSRI <sup>26</sup>, at least 20% of patients with MDD do not experience a remission after AD therapy <sup>27</sup>, in Bipolar Depression, finally, mood stabilizers and atypical antipsychotics may provide only suboptimal relief of depressive symptoms <sup>28</sup>. Moreover, for many diagnostic categories there is no licensed drug: in this case, if medications are needed, these are off-label by definition <sup>8</sup>. For example, SSRIs are often used to manage depression and anxiety symptoms, in addition to self-harm behaviours in patients with Intellectual Disabilities <sup>29</sup>. This is also the case for PDs, NCDs, sleep disorders that were consistently associated with higher off-label prescription in the present study.

Younger psychiatrists were found to be more prone to off-label prescription: they may be generally more prone to a so-called 'risky behaviour', i.e. the tendency to underestimate the possible risks and consequences associated with off-label prescription, out of greater clinical inexperience, but they also may have a less rigid clinical attitude. Also, younger specialists may have access to a wider range of information, leading to higher pressure to implement off-label prescription in their clinical practice. Last but not least, higher levels of burnout syndrome described among young psychiatrists may impact also on their prescriptive style <sup>30</sup>.

A higher tendency to off-label prescription was also associated to personal clinical experience as motivation: the risks connected to overestimation, excessive self-confidence or being self-referential are well-known and described <sup>31</sup>.

Finally, the attitude toward off-label prescription was found to be associated with the tendency to rely on information received by pharmaceutical representatives.

**TABLE II.** Results of the multivariate regression analysis. Dependent variable: off-label prescription declared as "often".

	O.R.	95.0% C.I.		P-value
		Lower	Upper	
Age	10.53	2.13	52.13	< 0.01
SGAs-PDs	0.08	0.02	0.36	< 0.01
Personal clinical experience	0.05	0.01	0.36	< 0.01
Pharmaceutical representatives	0.58	0.01	0.31	< 0.01

Considering that representatives from pharmaceutical industries should only describe on-label approved use and indications of their Company's medications, this finding may reflect a tendency of clinicians in applying the information received more broadly, possibly as a result of limited pharmaceutical options to deal with very challenging clinical situations, as already discussed<sup>32</sup>. A clear need for non-sponsored and ethical clinical research and training over this topic emerges as a significant result of the study here discussed.

Several limitations affecting the present research need to be acknowledged. First, we enrolled a purpose sample of psychiatrists, and no random selection procedures were used other than the systematic inclusion of all online sources. Moreover, only psychiatrists working in the Region Emilia-Romagna and operating in private contexts of care were invited to take part to the study. This led to a sample size of 50 professionals, that may not be representative for the entire Italian population of psychiatrists. These recruitment procedures partly impair the generalizability of our findings. The choice to rely on the online delivery of an *ad hoc* questionnaire,

used to maximize feasibility, could have introduced response and self-selection biases, i.e. selection of a younger and more "technology-prone" sample of respondents. Despite all this, we obtained results in line with current literature on this topic, and particularly to one of the few existing similar studies performed in Italy<sup>33</sup>. Also, the present research was intended as pilot study for a nation-wide data collection currently on our research agenda, which aims to overcome the limitations hereby recalled.

## Conclusions

Off-label prescription of psychotropics is common among psychiatrists working in private practices. It is favoured by younger professionals, that frequently rely, when prescribing, on their previous personal clinical experience; off-label prescriptions are more often associated to the treatment of some diagnostic groups, e.g. PDs. A need for extensive and detailed clinical research and training activities on this topic emerged, to be taken into account in the next future.

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## Musical anhedonia: a review

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### SUMMARY

#### Objectives

Anhedonia, or the inability or the loss of the capacity to experience pleasure, is a core feature of several psychiatric disorders. Different types of anhedonia have been described including social and physical anhedonia, appetitive or motivational anhedonia, consummatory and anticipatory anhedonia. Musical anhedonia is a rare condition where individuals derive no reward responses from musical experience.

#### Methods

We searched the PubMed electronic database for all articles with the search term “musical anhedonia”.

#### Results

A final set of 12 articles (six original research articles and six clinical case reports) comprised the set we reviewed.

#### Conclusions

Individuals with specific musical anhedonia show normal responses to other types of reward, suggesting a specific deficit in musical reward pathways. Those individuals are not necessarily affected by psychiatric conditions, have normal musical perception capacities, and normal recognition of emotions depicted in music. Individual differences in the tendency to derive pleasure from music are associated with structural connections from auditory association areas in the superior temporal gyrus to the anterior insula. White matter connectivity may reflect individual differences in the normal variations of reward experiences in music. The moderate amount of heterogeneity between the reviewed studies is a limitation to the generalizability of our conclusions.

**Key words:** music, anhedonia, review

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#### Conflict of interest

The Authors declare no conflict of interest

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### Introduction

Anhedonia means “without pleasure” and is derived from the Greek an-, “without”, and hēdonē, “pleasure”. The term was coined by Ribot<sup>1</sup> to describe the inability or the loss of the capacity to experience pleasure. Progress in affective neuroscience challenged Ribot’s concept of anhedonia<sup>2</sup>, for example Thomsen and colleagues<sup>3</sup> suggested it as “impairments in the ability to pursue, experience, and/or learn about pleasure, which is often, but not always accessible to conscious awareness”.

Anhedonia is a psychopathological feature of several psychiatric disorders. It is a core feature of major depressive disorder and a prominent negative symptom of schizophrenia. Anhedonia has also been identified in substance-related and addictive disorders, eating disorders, maladaptive and risky behaviors, and Parkinson’s disease<sup>4</sup>.

Anhedonia has been differently considered as a pre-morbid personological characteristic (trait anhedonia) or as an acute symptom (state anhedonia) of the clinical picture of schizophrenia and major depressive disorder<sup>5</sup>. Recent investigations highlight the importance to distinguish between the differential effects of chronic, trait-like anhedonia and acute, state-like anhedonia on suicidal ideation and behaviors<sup>6</sup>.

Different types of anhedonia include social and physical anhedonia, sexual anhedonia, musical anhedonia, appetitive or motivational anhedonia, consummatory anhedonia, and anticipatory anhedonia. Physical anhedonia is an inability to feel physical pleasures while social anhedonia is an incapacity to experience interpersonal pleasure<sup>7</sup>. The hedonic process encompasses both anticipatory and consummatory components<sup>8</sup>. Consummatory pleasure reflects the momentary pleasure that is experienced while engaged in an enjoyable activity, while anticipatory pleasure revolves around pleasure from future activities. So, consummatory anhedonia is not enjoying the activity itself, while anticipatory anhedonia is the inability to experience any excitement about the future. In order to explore this two components of the experience of pleasure Gard and colleagues<sup>9</sup> developed the Temporal Experience Pleasure Scale, consisting of a subscale of anticipatory pleasure and a subscale of consummatory pleasure<sup>10</sup>. Other investigators differentiated deficits in the hedonic response to rewards (consummatory anhedonia) and a diminished motivation to pursue them (motivational anhedonia)<sup>11</sup>.

Our review focuses on musical anhedonia. Music is not considered to be a primary reward even if its role as a pleasurable stimulus is widely established<sup>12,13</sup>. Music is celebrated and valued in every human culture, and different hypotheses about its origins and cultural roles remain a subject of debate. Music perception and cognition researchers<sup>14</sup> posit that music serves many adaptive functions<sup>15,16</sup>, serving as an auditory channel for interpersonal communication, possibly preceding speech and language<sup>17</sup>. Thus, individual differences in the capacity to enjoy music could also have an evolutionary role for communication. Music is a form of communication incorporating strong emotional signals conveyed by the auditory channel.

In human evolution, music may have served to directly link auditory inputs and outputs with social and emotional reward centers<sup>14</sup>. Music may have also served a selective advantage in mate selection<sup>18</sup>. There are tremendous individual differences in the reward value of music and some individuals find music more pleasing than others<sup>19</sup>. At one extreme end of the spectrum is musical anhedonia, a rare condition where individuals derive no reward responses from musical experience<sup>20,21</sup>.

Further, individual differences in anhedonia occur in clinical and non-clinical populations<sup>21,22</sup>.

As reported by Oliver Sacks<sup>23</sup> in his book *Musicophilia*, loss of interest in music (finding it emotionally flat while retaining all of their musical perceptions and skills) is common after strokes, and such losses or distortions of musical emotion are more common with damage to the right hemisphere of the brain.

By reviewing available literature about music anhedonia we aim to clarify whether such a rare clinical condition could give us additional information on the complexity of the functioning of the musical phenomenon and its neural bases, in particular how the brain circuits that process the sound relate to the circuits that process the emotions, or how music can become an emotional experience.

## Methods

We searched the PubMed electronic database for all articles up to December 21<sup>st</sup>, 2018 with the search term “musical anhedonia”. The search included all languages. We compiled articles that (1) were published in English, Italian or French (2) provided empirical data (as opposed to reviews or commentaries). Two blind investigators (FB and LA) performed the literature search, title/abstract screening, full-text review. The selected references were cross-checked and the reference list of relevant articles was screened in order to search for additional literature. In addition we performed an independent review of other sources (e.g. books). Discrepancies were resolved through consensus.

## Results

Sixteen articles<sup>12-14,20,24-35</sup> were identified. We excluded two articles that were unrelated to the topic<sup>24,30</sup>, one comment<sup>27</sup>, one review article<sup>29</sup>, one article in Japanese<sup>35</sup>, and one article translating and validating a questionnaire to assess musical anhedonia<sup>31</sup>.

In addition to the PubMed search, two other relevant clinical case reports<sup>36,37</sup> of patients presenting musical anhedonia were identified. A final set of 12 articles, six original research articles<sup>12,13,20,26,33,34</sup> and six clinical case reports<sup>14,25,28,32,36,37</sup>, comprised the studies reviewed.

Five original research articles<sup>12,13,20,26,34</sup> focused on healthy individuals, while one<sup>33</sup>, the largest sample-sized study, focused on 78 patients with focal brain damage without pre-morbid neurological or psychiatric conditions. Table I summarizes the six original research articles.

All six single-case reports<sup>14,25,28,32,36,37</sup> described patients presenting musical anhedonia after focal brain damage, including one<sup>14</sup> which described “severe musical anhedonia” in a subject without clearly identifiable cortical lesions but a lower white matter abnormality between auditory system and reward connectivity. Table II summarizes patients’ characteristics and abilities, the clinical features of their musical anhedonia, diagnosis and site of lesions.

**TABLE I.** Summary of the original research articles on Musical Anhedonia (MA).

Article	Sample characteristics	Study characteristics	Main findings
Keller et al., 2013	21 healthy adults (M = 9, F = 12, ages 18-52) without current or past Axis I psychiatric disorders	fMRI with musical stimuli was used to examine brain responses and effective connectivity in relation to individual differences in anhedonia	Trait anhedonia was negatively correlated with pleasantness ratings of music stimuli Trait anhedonia was negatively correlated with activation in right NAc, basal forebrain and bilateral hypothalamus. Significant negative correlations were detected in the OFC, anterior insula, anterior and posterior cingulate cortex, and ventromedial prefrontal cortex Effective connectivity between NAc, VTA and paralimbic areas, that regulate emotional reactivity to hedonic stimuli, was negatively correlated with trait anhedonia. Trait anhedonia were not correlated with auditory cortex responses
Mas-Herrero et al., 2014	3 groups of 10 healthy individuals without depression or generalized anhedonia, each with high, average, or low sensitivity to musical reward, assessed using the Barcelona Musical Reward Questionnaire (BMRQ)	Participants performed a music task in which they had to rate the degree of pleasure while listening to pleasant music and a monetary incentive delay task In order to have objective physiological measures of emotional arousal, skin conductance response (SCR) and heart rate (HR) were recorded Music emotion recognition were tested 1-year later a follow-up session were performed with 26 out of the 30 participants	No differences among groups in the ratings (evaluation of pleasure for sex, food, money, exercise and drugs, but a significant effect on the music scale ( $p < .001$ ) Individuals with low BMRQ scores had the fewest high-pleasure or chill responses while listening to pleasant music. Similar results were obtained during the follow-up session. This result was also reflected by their relative lack of physiological responses (SCR and HR) Differences among groups could not be explained by deficit in music perception (amusia), in familiarity, nor in recognizing emotions in music
Martinez-Molina et al., 2016	3 groups of 15 university students (8 females and 7 males each), each with high, average, or low sensitivity to musical reward assessed using the BMRQ. All participants were nonmusicians and matched in age, general anhedonia, sensitivity to punishment and reward scale, and amusia score	SCR were recorded while participants listened to excerpts of pleasant, neutral, and unpleasant music fMRI was scanned while subjects performed a music listening test and a monetary gambling task	The music anhedonic participants showed selective reduction of activity for music in the NAc, but normal activation levels for the monetary gambling task. This group also presented decreased functional connectivity between the right auditory cortex and ventral striatum (including the NAc) In contrast, individuals with greater than average response to music showed enhanced connectivity between these structures
Mallik et al., 2017	15 healthy adults (M = 6, F = 9)	Naltrexone (50 mg) or placebo was administered on 2 different days in a double-blind crossover study Participants' responses to music were assessed using both psychophysiological (objective) and behavioral (subjective) measures	Naltrexone caused decreased physiological reactions to music for both pleasurable and neutral music compared to placebo Naltrexone caused a decrease in self-report measures of pleasure for pleasurable music but not neutral music



TABLE I. *continue*

Article	Sample characteristics	Study characteristics	Main findings
Belfi et al., 2017	78 patients with focal brain damage (M = 37, F = 41, mean age = 59.2) without premorbid neurological or psychiatric dysfunction, and no history of alcohol or drug abuse	Musical anhedonia, anhedonia for different behaviors, and music perceptual abilities were assessed with mailed questionnaires and in-lab task	5 patients showed signs of MA. None of these patients had signs of general anhedonia. The lesions locations for these patients were varied and included: ventromedial prefrontal cortex, posterior cingulate cortex, left temporal pole, and striatum No clear or consistent neuroanatomical correlates of MA were identified One patient with damage to the right hemisphere putamen and internal capsule displayed specific and severe acquired MA
Mas-Herrero et al., 2018	39 healthy subjects, classified into three groups of 13 individuals, according to their Barcelona Music Reward Questionnaire (BMRQ, Mas-Herrero et al., 2013): – 13(6)ANH_specific musical anhedonics, BMRQ < 65 – 13(7)HDN_musical hedonics, 65 < BMRQ < 87 – 13(9)HHDN_musical hyperhedonic, BMRQ > 87 (number of female in parenthesis)  The subject were matched in sex and age; They presented similar scores in hedonism as measured by the Physical Anhedonia Scale	Participants performed two tasks: – an aesthetic task(a series of 56 pictures of paintings from Cattaneo et al., 2014, and Cela-Conde et al., 2004, 2009, after which participant should evaluate the amount of <u>pleasure</u> (on a scale from 1- "I found it unpleasant" to 7- "I liked it a lot," where 4 was "I neither liked nor disliked it"), <u>arousal</u> (on a scale from 1 to 5), and <u>familiarity</u> (on a scale from 1 to 5) experienced with that painting – an emotional sounds task (30 different sounds, selected from the International Affective Digitized Sounds, IADS-2, Bradley and Lang, 2007), after which participant should rate the degree of pleasure and arousal experienced.  During both tasks skin conductance response (SCR) was recorded using two AgAgCl electrodes using a BrainVision BrainAmp device. The electrodes were attached to the forefinger and the ring finger of the left hand The level of SCR was the mean SCR amplitude after stimulus or response onset with respect to baseline (500 ms). SCR amplitude was determined in the 0-15s windows after the presentation of a painting or an emotional sound	Specific musical anhedonics showed similar hedonic reactions, both behaviorally and physiologically, as the HDN control group in both tasks  Post hoc analysis revealed that HHDN individual reported higher liking rates than the ANH (P = 0.002) and the HDN group (P = 0.038) but no differences were found between the ANH and the HDN (P = 0.46)  Pleasant paintings evoked more SCR amplitude among all participants and that this effect was independent of their music reward sensitivity  In the emotional sound task, there were no statistically significant differences among group means as determined by one-way ANOVA, neither in liking, nor in arousal rating  These findings suggest that music hedonic sensitivity might be distinct from other human abstract reward processing and from an individual's ability to experience emotion from emotional sounds

The results shown in tables highlight an important fact: that the brain areas involved in musical anhedonia, whether we talk about healthy individuals, whether we consider subjects with brain damage, are also widely involved in the elaboration of emotions and reward in connection with more specific auditory circuits (superior temporal gyrus in Loui's)<sup>14</sup>. In addition to the musical anhedonia, a behavioral response of reduced reactivity (emotional arousal) is also associated, given concordance with the reduced function of

the brain circuits that elaborate emotions. These areas are roughly located in the medial brain and include the medial temporal lobes, the temporal poles, the orbitofrontal cortex, the cingulate cortex, the insula, the nucleus accumbens and certain basal ganglia (e.g. striatum in Zatorre's)<sup>29</sup>.

## Discussion

Results show that musical anhedonia is related to dif-

**TABLE II.** Characteristics of 5 case reports of patients with MA.

Article	Age, gender, handedness, musical history	Diagnosis	Site of lesion	Clinical features of MA	Patient's characteristics and abilities
Mazzoni et al., 1993	24, M, Ambidextrous, Amateur guitarist	Haemorrhage due to an arterio-venous malformation	Right temporo-parietal, including the plica curva and supramarginal gyrus	Loss of aesthetic pleasure from listening to music ("music is flat, it's no longer 3-dimensional, it's only on two planes")	Neurological examination, tonal audiometry, neuropsychological and neuromusicological examinations were normal
Griffiths et al., 2004	52, M, R, np	Infarction	Left insula, partly extending into the left frontal region and left amygdala	Loss of pleasure from listening to particular pieces of classical music	No anhedonia in different domains. No depression. Neuromusicological assessment was normal
Satoh et al., 2011	71, male, R, np	Infarction	Cortical and subcortical regions of the right inferior parietal lobule, including both the angular and supramarginal gyrus	Unable to experience emotion in listening to music. He described music as dull and lacking freshness	Neuropsychological assessments were normal. Speech audiometry and recognition of environmental sounds were within normal limits. Neuromusicological assessment revealed no abnormality in the perception of elementary components of music, expression and emotional perception of music. Psychiatric assessment was normal
Hirel et al., 2014	43, male, R, amateur	Infarction	Right ischemic lesion affecting the superior temporal cortex, in particular lateral Heschl Gyrus and the posterior part of the Superior Temporal Gyrus (Brodmann areas 21 and 22)	Loss of interest for music and lack of emotion in listening to music, associated with amusia	Hamilton Depression Scale was normal. No anhedonia in different domains than music. Mild auditory impairment for high frequencies (> 2000 Hz) Montreal Battery for the Evaluation of Amusia: total score = 21.3/30, with pathological score in tonality, pause, and prosody. Montreal Evaluation of communication was normal. Evaluation of emotion perception (for faces and music) showed a severe impairment of musical emotion



TABLE I. *continue*

Article	Age, gender, handedness, musical history	Diagnosis	Site of lesion	Clinical features of MA	Patient's characteristics and abilities
Satoh et al., 2016	63, M, R, professional chorus conductor	Putaminal hemorrhage	Subcortical region of right temporal lobe. Subcortical fiber degeneration between the superior temporal gyrus and the posterior two-thirds of the right insula. Decreased regional cerebral blood flow in the right insula and temporal lobe	Unable to have any emotional experience while listening to music. Sound was described as dull and lacking freshness	No hearing deficit No anhedonia in different domains Neuropsychological examination was normal Normal speech audiometry and environmental sound recognition Normal perception and expression of music Impairment of judgment of "musical sense" Inability to discriminate the sound of chords in pure versus equal temperament Impairment listening to the inner vocal parts, such as alto and tenor, while conducting a chorus, and when experiencing the cocktail party effect during conversation Intact response to visual and other auditory stimuli and sensory modalities
Loui et al., 2017	53, M, R, np but 4 years of musical training started from the age of 13; versus 46 controls (17 F), 20.5 age, R, 7.3 y of musical training	None specific lesion reported	Decreased white matter but higher Fractional Anisotropy (FA) between auditory and reward areas, in detail: <ul style="list-style-type: none"> <li>– lower tract volume between left Superior Temporal Gyrus (STG) and left Nucleo Accumbens (NAcc); left Anterior Insula and left NAcc</li> <li>– Mean FA was greater between left STG and left AIns</li> </ul>	A self-reported, socially debilitating lack of reward experience from music (intact reward responses to visual art) BMRQ (Music Reward overall score)-9, 5.89 standard deviation below controls	PAS (Physical Anhedonia Scale): <ul style="list-style-type: none"> <li>– Not anhedonic except for items that pertain to sounds</li> <li>– Montreal Battery for Evaluation of Amusia and the nonverbal measure of the Shipley Institute of Living Scale were used to rule out any differences due to amusia or general intellectual impairment, respectively (results similar to controls)</li> </ul> No other information about Neuropsychological or Psychiatric assessment

ferent patterns of connectivity from auditory to emotion and reward centers of the brain. This auditory access to the reward system informs the evolutionary basis of music: perhaps music evolved as a direct auditory pathway toward social and emotional reward centers in the

brain. Building on to Patel's Transformative Technology of the Mind (TTM) theory, the Mixed Origins of Music (MOM) theory posits that music transforms the brain through an affective signaling system common to many social animals<sup>38,39</sup>.

Music can effectively elicit highly pleasurable emotional responses<sup>40</sup>. Neuroimaging and noninvasive brain stimulation studies identify activation of brain emotion and reward circuits during pleasurable music listening<sup>12,13,41-46</sup>. The “liking” and “wanting” components<sup>26</sup> that are lacking in anhedonia<sup>47,48</sup> may result from dysfunctions in limbic reward system (MRS) and its associated pathways<sup>49</sup>. The main brain areas of the reward system are the nucleus accumbens (NAc), septum, and the ventral tegmental area/substantia nigra (VTA/SN)<sup>50,51</sup>, which are interconnected by the medial forebrain bundle (MFB). In VTA, the mesolimbic dopamine neuron cell bodies reside and project to the NAc, and dopamine release in VTA is crucial for reward processing<sup>52</sup>. The MFB connects the VTA to the NAc as well as to other basal forebrain (eg, septum) and frontal lobe regions involved in reward and motivation<sup>53</sup>. Mesolimbic and mesocortical pathways involving the VTA, NAc, amygdala, septum, orbitofrontal cortex and medial prefrontal cortex are involved in reward processing, anticipation and learning<sup>54-56</sup>. According to Zatorre<sup>29</sup> perhaps musical reward is different, given its complex and abstract nature, and given its important dependence on cultural factors and learning. As such, music reward may depend to a greater extent on cortical mechanisms than other more basic ones. Musical reward may be mediated via cortical mechanisms in interaction with subcortical system, so that music reward value increases as a function of enhanced functional interactions between the striatum and a temporofrontal cortical network<sup>29</sup>. There are marked individual differences in the reward value of music and some individuals find music more pleasing than others<sup>19</sup>. These differences extend to both spectral ends: excessive pleasure from music (“musicophilia”) and on lack of pleasure from music (“musical anhedonia”). Congenital musical anhedonia occurs in approximately 5% of healthy adults<sup>19,20,33</sup>. These individuals derive no pleasure from music, both in self-reported ratings and physiological responses<sup>20</sup>. Acquired anhedonia for specific stimuli or behaviors occurs in rare patients with neurological damage (eg, anhedonia for smoking)<sup>57</sup>. Music-specific anhedonia is especially rare. While the types of music that are considered pleasurable vary considerably within and between cultures, the vast majority of people enjoy some forms of music some of the time. People with musical anhedonia show diminished emotional arousal on autonomic measures such as skin conductance response (SCR) and heart rate measurements compared with people with average or high sensitivity to music. Individuals with musical anhedonia show normal responses to other types of reward<sup>12</sup>. This condition was termed specific musical anhedonia since the patients are hedonically responsive to other rewards, suggesting a

specific deficit in musical reward pathways<sup>13</sup>. Those individuals are not necessarily affected by psychiatric conditions (eg, depression or generalized anhedonia), have normal musical perception capacities, and have normal recognition of emotions depicted in music. Do different types of aesthetically related stimuli activate the same neuronal circuits? Yes, similar to music, emotional responses to pleasant paintings activate regions implicated in reward processing such as the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the striatum<sup>58-60</sup>. Pleasant visual art and music engage overlapping structures, including the OFC, the ACC, and the striatum, which are also involved in the processing of primary and secondary rewards<sup>59-61</sup>. What differs is probably the route to access a common reward circuit. In music, the processing of time and sound is critical: listening to music engages high-order cortical structures including the auditory cortex<sup>62,63</sup> as well as the frontal regions to which it connects, such as the inferior frontal gyrus, crucial for working memory and predictive coding<sup>64-66</sup>. It is still unclear whether a uniform abstract aesthetic reward network, including musical and visual aesthetics, exists; and if so, if musical anhedonia reflects a dysfunction of this network. The network implicated in the experience of musical perception and reward is posited as the nucleus accumbens (NAc), involved in reward and affective processing, the superior temporal gyrus, crucial for music perception<sup>12</sup> and their interconnections and connections with other reward system areas, such as ventral striatum, caudate, dorsal striatum, and limbic areas (eg, amygdala and anterior insula)<sup>44,45</sup>. Individual differences in the tendency to derive chills, i.e., measurable psychophysiological responses, from music are associated with structural connections from auditory association areas in the superior temporal gyrus to the anterior insula (AIns)<sup>14</sup>, which is consistently activated when experiencing strong emotions, and the medial prefrontal cortex (mPFC), important for computing social value. Furthermore, this association is modulated by connectivity through the NAc, a hub in the dopaminergic reward system<sup>67</sup>. Patterns of white matter connectivity in the auditory and reward systems reflect individual differences in the tendency to perceive reward from music. In Loui’s article<sup>14</sup>, the Music Reward score, among the controls, was significantly predicted by the volume of tracts between LSTG (left superior temporal gyrus) and LAIns (left anterior insula). Moreover auditory–reward connectivity differences are observed in the extreme case of musical anhedonia<sup>14</sup>. Fractional anisotropy, the main outcome variable in Diffusion Tensor Imaging (DTI), is an index of white matter integrity, which includes myelination and coherence of axonal bundles. The pattern of simultaneously increased white matter integrity and decreased volume may suggest increased myelination and/or decreased

crossing fibers in the MA subjects' anatomical connections between LSTG and left nucleus accumbens (LNAcc), which could result in increased inhibition from LSTG to LNAcc. Functionally, the increased inhibition from LSTG could lead to a down-regulation of the activity of LNAcc, resulting in deactivation of the NAacc as observed in recent functional MRI work in musical anhedonics<sup>12,14</sup>. Control subjects' data in Loui et al. article<sup>14</sup>, can predict the MA subject tract volumes but not his behavioral scores, as if he would lie at the low end of a normal distribution, as a very rare condition.

This is consistent with the observation that across patients of many types of brain damage, few report musical anhedonia<sup>33</sup>.

Something more specific must be said on the lateralization of music and emotion, which are both complex, variable among individuals, and bilaterally represented. Having said that, there is evidence from the data we reviewed, both fMRI in normal individuals and the Belfi paper<sup>33</sup> that show a greater predominance of right sided activation with musical appreciation/right hemisphere decreased activity with musical anhedonia, as well as greater predominance of right hemisphere lesions above in musical anhedonia cases.

In Loui et al.<sup>14</sup>, it is noteworthy that only tracts from left or right superior temporal gyrus (the only auditory regions in Loui's model) emerged as significant predictors, sug-

gesting that individual differences in music reward do pertain to auditory-specific access to the reward system and that auditory access to the mesolimbic pathway is hemispherically asymmetric, with normal variations in reward sensitivity occurring on the right but abnormal lack of reward on the left.

In this paper we attempted to briefly synthesise the small and heterogeneous literature on musical anhedonia, a rare but interesting condition with considerable relevance for neuropsychiatry. Several limitations deserve mention in this discussion. Surely, a major limitation lies in the fact that only PubMed electronic database was used for searching, suggesting the possibility of some missing papers; however, check of reference lists from selected articles was performed to identify articles missed by the initial search. Another limitation of this study is the moderate amount of heterogeneity (e.g., in study design, sample characteristics, screening instruments, diagnostic techniques) between the studies included in this review, so that conclusions should be interpreted cautiously, and future research is needed to further investigate the musical hedonia network. Whether music is found to be pleasurable or not (anhedonia) is associated with the reward system and structural connection development and integrity. Much remains to be learned, but it is conceivable that altered white matter connectivity may primarily or even exclusively impact the appreciation of music.

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# Psychiatric disorders and organ transplantation: an approach based on resources and resilience

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## SUMMARY

The article focuses on psychiatric disorders, which are becoming increasingly common among the general population, and their compatibility with the transplant journey. After analyzing part of the literature on the subject, an attempt was made to describe our approach with respect to the eligibility of the patient with a psychiatric disorder to a possible transplant, and the psychological path followed by our patient in order to “neutralize” as much as possible the psychological risk factors, and enhance the protective factors that can facilitate the treatment process. The approach used by the psychology service and shared by the care team is based on the opportunity to recognize, for each individual case, risk and protective factors with regard to the planned care path and, based on this, evaluate the possibility of a transplant. This approach has proved to be effective for the treatment of patients with a psychological disorder and who need to face complex but necessary treatments in terms of survival.

Through the description of a clinical case we try to exemplify the main points of the approach based on resources and resilience. The clinical case herein reported regards a woman suffering from alcohol-related liver cirrhosis and bipolar disorder undergoing a deceased donor liver transplant.

**Key words:** transplantation, psychiatric disorder, resilience, psychological assessment

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## Conflict of interest

The Authors declare no conflict of interest

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## Introduction

### The literature on organ transplantation in psychiatric patients

Psychiatric disorders are becoming increasingly common among the general population, therefore accounting also for a significant number in the population of patients with an end-stage organ disease requiring organ transplantation<sup>1</sup>. Some psychiatric disorders are reactive to the condition of a chronic disease requiring a transplant (depressive anxiety disorders) or are due to exacerbation of pre-existing disorders. Others are primitive to the state of a chronic disease or are even the cause (substance and/or alcohol addiction)<sup>2</sup>.

Mood and anxiety disorders are the most common disorder among the organ transplant patient population<sup>3</sup>. Many of these are pre-existing disorders, a phase in which the patient's quality of life is often significantly limited<sup>4</sup>. In the post-transplant phase, the risk of awakening a latent anxious depressive disorder is related to the stress associated with the complex care path and to the difficulties of adapting to the new clinical condition, as well as the immunosuppressive regimen<sup>5</sup>. Among anxiety disorders, post-traumatic stress disorder (PTSD) appears to be the most relevant one<sup>5</sup>. Psychotic disorders are more complex, based on what the literature suggests, and seem to be mainly connected to disorders already pre-existing in the pre-transplant phase. This brings attention to

the need for a careful assessment in the pre-transplant assessment phase in order to identify effective pharmacological treatments, and therefore avoid that psychotic symptoms may present in an acute form in the post-transplant phase, when they may have important repercussions on the therapeutic outcome <sup>6,7</sup>.

Increasingly often, the care team that determines a patient's eligibility for a transplant is faced with this question <sup>8</sup>. Can the successful outcome of the transplant and the improvement of clinical conditions improve/reduce the psychiatric symptoms of the potential transplant candidate? Or can such a psychiatric condition negatively affect the patient's post-transplant attitude, thus putting the successful outcome of the transplant at risk? The main national and international guidelines (Tab. I) seem to agree on the fact that a psychiatric disorder,

whether primary or reactive, cannot be an absolute contraindication to a transplant. However, it is necessary that the type and manifestation of the disorder be well assessed before the patient is listed for a transplant, carefully weighing his\her eligibility for the transplant journey in terms of lifestyle and compliance required <sup>9,10</sup>. The most commonly defined contraindications for solid organ transplantation on the basis of mental health include multiple suicide attempts despite full support, dementia, severe learning difficulties, medical non-compliance, active schizophrenia, and severe non-reactive depression. These problems must be considered in consideration of those factors that predict a favorable outcome, which include good cognitive function, adequate social support, and compliance with therapy <sup>11</sup>.

**TABLE I.** *Mental Health Disorders and Solid-Organ Transplant Recipients (from Corbett et al., 2013, mod.)* <sup>13</sup>.

Organ	Society	Absolute	Relative	Comments
Liver	American Association for the Study of the Liver Diseases (2) 2008  British Society of Gastroenterology	Continued destructive behavior resulting from drug and alcohol addiction  Nil	Significant psychiatric disorder must be under excellent medical control, with assurance that the patient can be compliant after transplantation, with adequate support from family and friends  Severe psychiatric disorder	
Heart and lung	International Society for Heart and Lung Transplantation (3) 2006	Active substance abuse	Mental retardation or dementia (class 2a); poor compliance with drug therapy (class 3)	Assessment concentrates on compliance, comprehension quality of life, and social evaluation (support)
Lung	American Thoracic Society (4) 1998	Nil mentioned	Poorly controlled major psychoaffective disorder, inability to comply with complex medication regimen, history of non-compliance with medical care or treatment plans even in the absence of documented psychiatric problem	Joint statement from International Society for Heart and Lung Transplantation, European Respiratory Society, and American Society for Transplant Physicians
Kidney	UK Renal Association (5) 2011  European Association of Urology (7) 2010	Nil mentioned	Living kidney donation also enables scheduling of transplantation at a time when the recipient is in optimal medical and psychological condition, and may be the only option in high-risk recipients  Psychiatric disorders for living donors and recipients	In use by NHS Blood and Transplantation  In use by NHS Blood and Transplantation

Patients with mental disorders, when adequately compensated from a symptomatological perspective and supported by an effective support network, have therapeutic outcomes comparable to those of the general population. Therefore, ruling out the transplant option based on the psychiatric diagnosis alone would be neither ethically nor clinically justified<sup>12</sup>. However, it can be ethically and clinically justified to deny access to transplantation to patients who, despite full relational support, would have an unacceptable quality of life or could not guarantee therapeutic compliance, thus risking losing the transplanted organ<sup>13</sup>. The greatest doubts regarding this problem concern the difficulties in predicting the repercussions that a transplant can have on the psychiatric symptoms even when they appear to be well compensated in the pre-transplant phase. The post-transplant path, is a highly stressful and unpredictable period in terms of possible complications, the required hospitalization period, and recovery time in terms of quality of life. Such discomforts, if intense and prolonged, could exacerbate the psychiatric symptoms or induce the patient to not fully adhere to the therapy, resulting in a psychiatric decompensation, thus jeopardizing the successful outcome of the transplant<sup>13</sup>. On the other hand, the same concern, though to a lesser extent, could also impact the population of non-psychiatric patients experiencing a particularly difficult and long post-transplant treatment course, thus causing strong emotional reactions to the point of manifesting significant psychiatric symptoms<sup>14</sup>.

## Description of activities and working methods

### The ISMETT clinical psychology service

At ISMETT, patients with end-stage organ failure with a transplant indication preliminarily undergo a psychological assessment in order to understand their overall psychological functioning, the social and relational context within which they live, and identify any psychopathological difficulties that could jeopardize the success of the transplant.

The assessment is mainly based on a psychological interview with the aim of retrieving an accurate medical history of the patient, creating a therapeutic relationship based on trust and collaboration, informing the patient about the transplant journey and detecting constraints and resources that can positively or negatively affect the treatment path. On some occasions it is necessary to deepen the initial psychological assessment with further in-depth interviews and, not infrequently, it is necessary to administer psycho-clinical tests or, in some cases, to refer the patient to a specialist psychiatric consult.

The first psychological assessment mainly investigates the following areas:

- awareness of the disease and motivation to treatment;
- acceptance and adaptation to the diagnosis of the disease;
- styles of coping and resilience;
- defense mechanisms and reactive modalities;
- therapeutic adherence;
- dysfunctional ideas regarding the disease and the care path;
- compatibility with expectations and personal values with respect to the envisaged life path;
- psychopathological/interpersonal area;
- presence of psychopathological/psychiatric disorders;
- abusive behaviors;
- aggressive conducts;
- past traumatic experiences not properly processed;
- disorders of the interpersonal and/or family sphere;
- social, interpersonal, emotional support area.

Based on the information collected, the patient's psychological eligibility for a possible transplant is determined. The patient who has absolute or relative psychological contraindications is referred, based on the specific goals to be achieved, to psychological/psychotherapy treatment within the ISMETT Psychology Service or the community. Also, based on the specific psychological scenarios identified, a personalized psychotherapy treatment is developed in order to limit as much as possible any factors of psychological vulnerability, as well as to further strengthen personal and family resources (see Figure 1).

### The approach based on resources and resilience

The greatest challenge of transplant psychology is the possibility, in the pre-transplant assessment phase, to carefully identify all those risk and protective factors that may hinder or facilitate the adaptation to the post-transplant condition.

Internationally, this approach is defined as a *vulnerability model*, representing a well-accepted conceptual framework to explain the development and outcome of psychiatric and psychosomatic disorders<sup>15</sup>.

The basic assumption of this model is that vulnerable people exposed to stress factors tend to have a poor psychosocial adaptation. Based on the so-called vulnerability indicators, it can therefore be possible to predict an inadequate adaptation. In transplant medicine, the assessment of the risk regarding post-transplant psychosocial adaptation plays an important role, and the identification of patients at risk is a major task of the pre-transplant psychosocial assessment.

However, to date, there are no studies identifying models or characteristics of the psychosocial variables that pre-

dict the post-transplant outcome. In the best case scenario, it is possible to test the prognostic validity of a few symptoms or isolated psychosocial variables in terms of post-transplant psychosocial or physical outcome<sup>15,16</sup>.

These reflections bring us back to the need to conduct an adequate and in-depth psychological and psychiatric assessment in the pre-transplant phase, but also to follow the patient accurately and consistently along the post-transplant journey, in order to prevent initial forms of discomfort that may turn into the onset of a psychiatric disorders. At the same time, this leads us to the possibility of grasping, already in the pre-transplant phase, not only the patient's limitations in terms of psychological and relational vulnerability, but also the resources that can be activated and used during the treatment process at an early stage, thus reducing the discomfort experienced by the patient before it translates into a full-blown psychiatric disorder.

This approach, basically based on resilience, is the one used by the Clinical Psychology Service.

More specifically, the approach based on resources and resilience is the one that is increasingly spreading within the field of psychology of health. This approach assesses and describes the psychological functioning of the person not only in nosographic diagnostic terms, but also in terms of functioning or malfunctioning of the individual or of the family system with regard to a given event<sup>17</sup>. The focus is shifted from the search for causes or culprits of the psychological distress to the accurate description of a psychological functioning. This is done with the aim of allowing a distinction between one form and another of discomfort and, above all, to understand the potential within each of the different forms of discomfort. This model of intervention encourages the psychotherapist, after identifying the traumatic experiences that have determined a psychological reaction, to investigate the resilient mechanisms that allowed the patient to overcome them<sup>17</sup>. In fact, the attitude of the clinician who, faced with psychopathological behaviors, is pushed to identify the functional and reparative value of the symptom, addressing the patient and the problem with an attitude of trust<sup>18</sup>.

### **A clinical case**

Barbara is a 42-year-old woman, divorced for 5 years, living with her two sons aged 16 and 5. She is the second child, and has 2 brothers. She was referred to our transplant center as she was suffering from decompensated alcohol-related liver cirrhosis, and during the clinical investigations she was also diagnosed with hepatocellular carcinoma. Her clinical history also showed a diagnosis of bipolar disorder.

Barbara comes to her first appointment showing an accelerated and disruptive speech, and a thought pattern characterized by fleeing ideas and high distractibility. She

has an eccentric look and is not very receptive to interactive feedback, with a prevailing egocentric and talkative language. She invades the therapeutic space with her strong emotionality, which is difficult to contain. Though the setting of the first assessment is oriented toward an initial pre-transplant evaluation, it is immediately clear that there is the need to create a functional therapeutic relationship in order to conduct a thorough psychological evaluation before expressing the patient's eligibility for a possible liver transplant. Barbara initially seems unable to understand the severity of her clinical condition while recognizing the dysfunctionality of the alcohol abuse behavior that caused the liver disease. In this regard, she explains this behavior as a reaction to the conflictual marital relationship resulting from the end of her marriage. Barbara reports that she was strongly hyper-involved in the dysfunctional relationship with her husband, who she defines as aggressive and violent, and whom she considered the cause of her alcohol addiction as well as the psychological breakdown that required psychiatric intervention. The patient reports being followed by a community psychiatrist who diagnosed her with bipolar disorder currently under pharmacological treatment. The onset of this disorder, which coincides with the end of her marriage, even if treated pharmacologically, has a frequent alternation of depressive episodes in which the patient remains in bed, in the dark, with hypomanic episodes in which she is euphoric and hyperactive.

The therapeutic attitude with the patient is to welcome and contain her with respect to the strong need to express her discomfort and suffering. But given her clinical condition, there is also the need to induce her to become aware of the state of illness, and to make her responsible for her dysfunctional behaviors (alcohol abuse, smoking, obesity) and the need for a change in lifestyle to manage the current clinical condition and, if necessary, be able to access a more effective treatment path.

After her suffering has been recognized, and she has been encouraged to regain control over her life, starting precisely from the state of illness, Barbara seems to show plausible intentions of collaboration and willingness to modify the dysfunctional relational balances at the basis of her malaise. However, her availability and motivation inevitably clash with her psychiatric disorder, not yet well compensated pharmacologically, with continual mood changes. Therefore, the next therapeutic step becomes that of creating a close and effective collaboration with her psychiatrist in order to reach a condition of psychiatric compensation that is fundamental to the continuation of the psychotherapy with the patient. Psychiatric compensation is achieved a few months after the first appointment, and stable monitoring by the ISMETT Psychology Service and Territorial Psychiatric Service. Barbara begins to become fully aware of her

clinical and life condition, clings to her parental role and the need to be a present and competent mother for her children to find the motivation to care, and also to start projecting herself with confidence into the future. Within a few months Barbara shows that she is gradually regaining possession of her life: she resumes taking care of her appearance and not only, taking care of her children carefully, managing her clinical condition and finding a balance even in relationships with the family of origin that shows itself to be supportive and ready to accompany the patient in the treatment path to be faced. Barbara is ready to undertake the transplant evaluation process, which will have to establish her eligibility for a liver transplant. After a careful diagnostic study, and given the compensation of the psychiatric disease maintained over time, the patient is deemed clinically suitable for inclusion on the waiting list.

However, the final decision regarding this clinical choice goes through a multidisciplinary discussion of the complex case, and this moment of exchange is strongly conditioned by the information on the patient's psychiatric state. The fear that a new psychiatric failure may compromise the successful outcome of the transplant puts the entire care team in crisis, and is divided between those who confidently welcome the psychological improvements that have occurred and those who, with skepticism, feel the responsibility not to waste a treatment path that involves the use of an organ, a precious and limited resource for each transplant center. The principal guidelines and the most recent scientific evidence in this area refer the final decision to the evaluation of the individual case and the responsibility of the care team. Faced with this difficult decision by the care team, the need to re-evaluate the information available by re-reading it in a new epistemological light becomes clear: therefore the case of Barbara, initially described as the case of a patient suffering from hepatocellular carcinoma with alcohol-related liver cirrhosis and bipolar disorder that requires hepatic transplantation, is re-interpreted as the case of a young woman and mother, suffering from a serious organ disease, the prognosis of which, without the transplant, would be highly unfavorable and who, despite being affected with a major psychiatric disorder, shows a well-compensated status in this regard (normothymia), with good compliance intentions and a supportive family. An approach aimed at seizing the healing and functional potential of the person and her family system allows for doubts about the continuation of the patient's care path to be resolved, allowing the team to grasp the critical issues but also the available resources. The careful re-evaluation of the peculiarities of the clinical case guides the multidisciplinary team to take responsibility for proceeding with the inclusion in the list, aware of the need to treat the case

with particular attention and competence, but confident of being able to offer the woman the possibility of taking advantage of a treatment path not precluded by a psycho-diagnostic label.

After a few months Barbara undergoes a liver transplant: she faces a post-transplant path that is not particularly complicated with a good therapeutic outcome. She is welcomed by a care team ready and prepared to face any difficulties or complications, not only clinical but also psychological, and this allows the patient to feel that she is taken in care globally, perceiving herself as a member of the care team, and therefore responsible in the first person of her behavior and her collaboration. Barbara has now been transplanted for 7 months, she is closely monitored by the ISMETT Clinical Psychology Service and by the territorial mental health center. The woman takes her youngest child to the first day of school, has regained some friendships and projects herself into the future with confidence, appreciating the newly found state of health. The past months have not been free of difficulties or therapeutic and psychiatric unforeseen events, however, Barbara and her family have always shown themselves capable of recognizing any moments of fragility and have been able to ask for help, and collaborate in the management of any problems.

Though we are aware that the time elapsed since transplantation is still too short to express ourselves, we are convinced that any difficulties or problems that we will face are comparable to those of other patients who face a complex path of care in conditions of psychological vulnerability, but who manage to take possession of the healing potential inherent in the same treatment path, while also reiterating the importance that in this, as in other cases, the active support of the family is paramount.

## Discussion

The clinical case reported here leads to a series of important reflections, starting with the awareness that the choice about transplant eligibility of a patient is a complex decision-making process that requires some important steps:

- possibility/opportunity for a constant and constructive exchange of views within the multidisciplinary team;
- identifying the most appropriate path of care, taking into account the benefit of each specific patient not only in terms of survival but also in terms of quality of life;
- not underestimating, from a psychological standpoint, the patient's peculiar and unpredictable reactive abilities triggered by emotionally restructuring events, such as a transplant.

In fact, we believe that the decision on the transplant eligibility of a patient must consider various levels of anal-

ysis: clinical choice, life prospects in terms of survival, quality of life, and risks/benefits of the care path for that specific patient, taking into consideration the values of the patient and his support system, etc. The indication for a specific care path, in fact, starts from a careful diagnosis and clinical prognosis, but must necessarily consider the patient's ability to give meaning to the disease, his/her motivation to treatment and to resume life plans, complying with the care path proposed by the clinical team. In this sense, we believe that every treatment must be designed and tailored to the patient, who must manage it in line with his path and life expectancy. This decision-making process, therefore, cannot be the task of a single professional, but must use all the care professionals who know the patient, his/her illness, his/her motivation for treatment, and his/her potential for adapting to the treatments offered.

Finally, we believe that valid guidelines on psychological indications and contraindications to transplantation must certainly look for those variables that predict a therapeutic success or failure. However, they cannot fail to take into account the potential inclination of every human to change and to adapt to highly stressful situations. This consideration makes the transplant process an emotionally restructuring event capable of reorganizing the psychological and relational balance of the individual who faces it.

## Conclusions

This paper intends to bring attention to the issue of psychiatric disorders as a possible contraindication to transplantation, proposing a specific modality of pre-transplant psychological assessments of patients with psychiatric comorbidities. The scientific evidence and our clinical experience guide our psychotherapeutic actions towards a psycho-diagnostic approach based on the patient's overall care and on the possibility of recognizing the modalities of functioning and malfunctioning with respect to the care path to be addressed. The clinical case described shows how an adequate assessment of protection and risk psychological factors, combined with an accurate multidisciplinary assessment, has allowed a young woman to access an effective care path that likely would have been denied to her within a rigid decision-making model unable to re-read information and events in a constructive way. Hence the desire to launch a message of "change" to the scientific community that deals with transplants, of re-reading the psychological assessment criteria through a new epistemological key aimed at seizing the underlying complexity of each person.

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## Safety and tolerability of Paliperidone Palmitate: a case report of an accidental overdose

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### SUMMARY

Paliperidone is a second-generation antipsychotic used in the treatment of Schizophrenia. It is also available as Paliperidone Palmitate (PP), a long-acting injection that can be administered monthly (PP1M) or every 3 months (PP3M). To our knowledge, only one case of PP accidental overdose has been described in Literature. We report a 55-year-old male who accidentally received a cumulative dose of 200 mg of PP within 5 days. The mistake was promptly recognized and this allowed a careful follow-up over the following hours and days. Clinical evaluation, supported by blood and instrumental tests, showed no medical consequences and the patient never complained of side effects. No additional therapy was required. Our experience, supported by data from the literature, suggests that PP is generally well tolerated and safe. However, a close clinical follow-up during the hours and days following an accidental overdose is recommended.

**Key words:** paliperidone palmitate, accidental overdose, long-acting injectables, case report

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### Conflict of interest

The Authors declare no conflict of interest

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### Introduction

Since the end of last century, a new class of antipsychotic drugs named atypical or second-generation antipsychotics (SGAs) was launched on the market: these molecules represent the first choice in the treatment of Schizophrenia, given their efficacy and tolerability. This led to the development, for some of the SGAs, of depot formulations called Long-Acting Injectables (LAIs). Currently, SGAs available in a LAI formulation are Risperidone, Olanzapine, Aripiprazole and Paliperidone. Paliperidone Palmitate (PP) is the only LAI available both in monthly (PP1M) and 3-monthly (PPM3) injection. This paper consists in a case report of PP1M accidental overdose: to our knowledge, such occurrence is reported only once in scientific literature<sup>1</sup>. We followed the CARE guidelines<sup>2</sup> in writing this case report.

### Case summary

The patient is a 55-year-old Italian male. He has been under the care of our mental health services since 2019. He initially received a diagnosis of Schizophreniform disorder and Antisocial personality disorder. After 6 months of clinical observation by our team, he met criteria for Schizophrenia. He does not have any medical comorbidities and he does not take any medications other than the prescribed psychiatric therapy. His clinical condition is characterized by positive symptoms (auditory hallucinations) that have been stable for several years. He also complains of low mood and a tendency to experience irritability and anger. His psychiatric history is characterized by severe impulsive behaviour, with episodes of harm toward himself as well as others. The patient was referred to our mental health services after being treated for several years in a psychiatric facility

of another Italian Region, where he was given Haloperidol Decanoate 75 mg monthly and Biperiden hydrochloride. During the first contact with our service, he complained of sexual side effects and lower limb tremors, asking to be switched to a different medication. For that reason, the patient was given oral Paliperidone that was well tolerated; he was then switched to PP1M. After he was given the first 150 mg injection and a second 100 mg injection 7 days later, he was put on a 4-week schedule of 75 mg of PP for 6 months. During this time the patient showed a good response to medication and maintained stable psychiatric conditions. After the outbreak of the COVID-19 crisis and the enactment of restrictive measures across Italy, the patient complained of irritability and severe anxiety. Therefore he was given an adjunctive anxiolytic intramuscular therapy (delorazepam) and, in correspondence of the seventh-month injection, the psychiatrist made the decision to increase PP dose to 100 mg monthly. Five days later the patient visited our mental health center again, asking to be given adjunctive anxiolytic therapy. However, due to a mistake in the interpretation of the prescription order, he was given a 100 mg injection of PP instead. The mistake was promptly recognized and this allowed a careful follow-up: the patient was rapidly evaluated by a physician that performed a complete physical examination and, in the following hours, he was periodically evaluated by a nurse who took vital signs resulting within the normal range all time. The psychiatrist requested an ECG registration with QTc measurement that was performed on the day following the accidental overdose, resulting in a normal trace and a QTc interval of 425 milliseconds. Moreover, a complete blood count, an electrolyte, liver and renal panel were performed. Results were all within range with the exception of a finding of microcytic anemia, unlikely linked to the accidental overdose. Clinical conditions were monitored on a daily basis through visits conducted both in person and by telephone. The patient never reported any side effect and denied to experience symptoms such as stiffness, anxiety or agitation. The psychiatrist administered a new PP injection 4 weeks after the accidental overdose.

## Discussion

Paliperidone (9-hydroxyrisperidone) is an active metabolite of Risperidone and it is an antagonist at D2 and 5HT2A receptors, as well as antagonist at  $\alpha$ 1,  $\alpha$ 2 and H1 receptors. This pharmacodynamic profile explains the potential occurrence of side effects such as orthostatic hypotension, weight gain and sedation, although to a lesser degree compared to Risperidone<sup>3</sup>. Moreover, Paliperidone has a lower propensity to cause anticholinergic adverse effects and cognitive impairment because of the absence of antagonistic activity at cholinergic receptors<sup>4</sup>.

Paliperidone is largely eliminated unchanged in urines. Cytochromes CYP2D6 and CYP3A4 do not seem to play a relevant role in the metabolism of Paliperidone in vivo<sup>4,5</sup>. From a clinical point of view, this translates into a low risk of drug-drug interactions.

PP formulation consists in nanocrystal molecules in an aqueous suspension that allows a slow dissolution after intramuscular injection: molecules are then hydrolyzed to Paliperidone and absorbed into the systemic circulation<sup>6</sup>. After a single dose, median time to reach  $C_{max}$  ranges from 13 to 17 days. The release of the active principle starts from day 1 and lasts for at least 4 months, while the median apparent half-life ranges from 25 to 49 days<sup>7-9</sup>.

PP most frequent side effects include insomnia, headache, dizziness, sedation, agitation, weight gain, tachycardia and extrapyramidal symptoms. Among these, akathisia and sedation/somnolence seem to be related to dose<sup>4,7</sup>. Although several cases of Paliperidone overdose are described in Literature, reporting consequences such as dystonia, acute renal failure, akathisia, and tachycardia<sup>10,11</sup>, there is only one PP overdose case description that reports no relevant consequences<sup>1</sup>. Moreover, several clinical studies showed that PP is a safe treatment even when used in high doses<sup>9,12,13</sup>, in addition to resulting well-tolerated and with low rates of discontinuation, mostly due to weight gain and increase in prolactin levels<sup>14</sup>.

This case report provides further evidence on the safety of PP, as no clinical consequences resulted in the administration of a total dose of 200 mg of PP within 5 days, requiring no additional or specific therapy. Specifically, we found no ECG alterations nor QT prolongation. However, we acknowledge some limitations to our case report. Firstly, compared to the other PP overdose case report<sup>1</sup>, the cumulative PP dose was lower and much closer to therapeutic dosages, so the fact we didn't find any clinical consequences could be expected, but not certain. Secondly, although the patient did not refer any symptoms ascribed to hyperprolactinemia, an evaluation of prolactin levels would have been useful. Unfortunately, the concurrent COVID-19 health crisis did not permit more tests than the ones already performed.

## Conclusions

Our experience, supported by data from Literature, suggests that PP is generally well tolerated and safe, especially when used as monotherapy. However, as in some cases Paliperidone side effects can be fatal, a close clinical follow-up during the hours and days following an accidental overdose is recommended.

## Consent

Oral informed consent was obtained from the patient for publication of this case report.

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