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Abstract:	Introduction: Panic disorder (PD) is a prevalent and impairing anxiety disorder with previous reports suggesting that the longer the condition remains untreated, the greater the likelihood of non-response. However, PD patients may wait for years before receiving a guideline-

recommended pharmacological treatment. The widespread prescription of benzodiazepines (BDZ) for managing anxiety symptoms and disorders might delay the administration of pharmacotherapy according to guidelines (e.g.: selective serotonin reuptake inhibitors, SSRIs). The present study aimed to determine the mean duration of untreated illness (DUI) in a sample of PD patients, to quantify and compare DUI-SSRI to DUI-BDZ, and to compare findings with those from previous investigations.

Materials and methods: 314 patients with a DSM-5 diagnosis of PD were recruited from an Italian outpatient psychotherapy unit, and epidemiological and clinical variables were retrieved from medical records. Descriptive statistical analyses were undertaken for sociodemographic and clinical variables, Wilcoxon matched-pair signed rank test was applied to compare the distribution of DUI-SSRI vs. DUI-BDZ, and Welch's t-test was performed to compare findings with those from previous studies.

Results: The mean DUI-SSRI of the total sample was 64.25 ± 112.74 months, while the mean DUI-BDZ was significantly shorter (35.09 ± 78.62 months; $p<0.0001$). A significantly longer DUI-SSRI, compared to findings from previous studies, was also observed.

Conclusion: The present results confirm a substantial delay in implementing adequate pharmacological treatments in PD patients, and highlight the discrepancy between recommendations from international treatment guidelines and common clinical practice in relation to BDZ prescription.

Original research

Latency to selective serotonin reuptake inhibitor versus benzodiazepine treatment in patients with Panic Disorder: a naturalistic study

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Abstract

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Key words: psychopharmacology, panic disorder, anxiety disorders, duration of untreated illness, treatment

Introduction

Panic disorder (PD) is typically a long-lasting condition, characterized by recurrent unexpected panic attacks, persistent worry about experiencing future attacks and their consequences and/or subsequent maladaptive changes in behavior [1]. It affects 1.6%-2.2% of the world population [2,3], with a lifetime prevalence of 1.5-5% [4] and a 12-month prevalence between 1.8-2.7% [5,6]. Previous investigations suggest that the longer PD remains untreated, the greater the likelihood of non-response [3]. Therefore, the duration of untreated illness (DUI), defined as the interval between the onset of a specific psychiatric disorder and the administration of the first appropriate pharmacological treatment according to guidelines in compliant subjects [7–9] may be a potential predictor of clinical course and outcome [10,11].

To date, DUI has been investigated across different psychiatric conditions, including major depressive disorder (MDD) [12–15], bipolar disorder [16], obsessive-compulsive disorder (OCD) [17–19], somatization [20], eating [21] and schizophrenia spectrum disorders [8,22–24]. In respect to anxiety disorders, previous reports indicate a significantly shorter DUI compared to findings from studies conducted with patients with obsessive-compulsive, mood, and schizophrenia spectrum disorders [9,25,26]. Moreover, differences in terms of latency to treatment emerged between patients with PD and generalized anxiety disorder (GAD), with PD patients having a shorter DUI [9,27]. Indeed, patients with PD may wait for years before receiving an adequate pharmacological treatment, with possible negative prognostic implications, such as a higher risk of developing comorbid MDD [11,13].

Nonetheless, only a few studies have assessed DUI in PD. A preliminary naturalistic study in a sample of 96 subjects attending an Italian outpatient clinic found a mean DUI of almost four years [28], while a more recent investigation involving a larger sample (n=138) showed a DUI of slightly more than 3 years [9]. Finally, a 4-5 years DUI was reported in an Italian multicenter study conducted on a sample

of 49 patients with PD[27]. Previous research has some methodological limitations, such as relatively small sample sizes, and the lack of assessment of potentially important variables related to psychopathological onset and latency to treatment, including type of first referral, presence of comorbidities and clinical presentation.

Focusing on pharmacological treatments of anxiety disorders and PD in particular, the widespread prescription of benzodiazepines (BDZ) as monotherapy might delay the initiation of guideline-recommended long-term treatments [29]. Treatment guidelines support the efficacy of selective serotonin reuptake inhibitors (SSRIs) or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine as first line pharmacological treatment of PD, and recommend caution for BDZ prescription due to associated risks of abuse, tolerance and withdrawal [30,31]. As little is known about the assessment and comparison between DUI-SSRI and DUI-BDZ in patients affected by PD, we sought to determine the mean DUI and related variables in a large sample of PD patients, with the additional aim of comparing findings with those from previous investigations in the field.

Methods

Study sample

A total of 314 patients with PD, who attended the outpatient psychotherapy unit of the Psychiatric Department of the Ospedale L. Sacco of Milan, Italy, between January 2015 and March 2019, was recruited. Data was retrospectively collected from patients' medical records. Patients had been diagnosed according to DSM-5 criteria by means of the Structured Clinical Interview for DSM-5 (SCID) [32] at the time of the first contact with the service. Subjects primarily affected by schizophrenia-spectrum disorders, unipolar or bipolar mood disorders, somatization, obsessive-compulsive and post-traumatic spectrum disorders, mild/major neurocognitive disorders and

anxiety disorders secondary to substance use or other medical conditions were excluded from the study. Comorbidity with personality disorders was allowed and assessed via the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) [33], administered by psychologists with specific training. Patients were interviewed after providing written informed consent for participation in the study and for having their clinical records examined for research purposes.

Assessment

Demographic and clinical variables collected during clinical interviews with patients (and, when available, relatives) were retrieved from medical records, including gender, age, education, age at onset, medical comorbidities, lifetime substance and alcohol abuse, age at first contact with psychiatric services, type of service at first contact (i.e., emergency department, psychotherapy unit, child and adolescent psychiatry unit [CAPU], general practitioner [GP], psychiatrist or other clinician), age at first pharmacological treatment, current pharmacological treatment, family history of psychiatric disorders and presence of agoraphobia or nocturnal panic attacks and prevalent type of panic attacks. As previously proposed [7,8,34], DUI-SSRI was defined as the interval (in months) between the onset of the disorder and the administration of the first adequate pharmacological treatment (i.e. SSRI), at an appropriate dosage and for an adequate period of time, in compliant patients, in agreement with international treatment guidelines[35,36]. Furthermore, DUI-BDZ, indicating the interval (in months) between PD onset and administration of benzodiazepines, was also calculated.

Statistical analysis

Descriptive analyses were carried out for sociodemographic and clinical variables of the total sample. Because of the non-Gaussian data distribution (assessed with the Shapiro-Wilk test), a nonparametric test (Wilcoxon matched-pair signed rank test) was applied to compare the distributions of DUI-SSRI *versus* DUI-BDZ. Welch's t-test was performed to compare results with findings from previous studies conducted by our group in independent samples. The level of significance was set at 0.05. Statistical analyses were performed using SPSS for Windows software (version 20; SPSS Inc., Chicago, Illinois, USA) and Prism (GraphPad Prism version 9.0).

Results

The main sociodemographic and clinical variables of the sample are summarized in Table 1 [Insert Table 1]. Male to female ratio was about 1:2, with a mean age of 42.55 ± 16.11 years. Of the 314 participants, 202 (64.3%) had a positive psychiatric family history, specifically for MDD in the 19.4% of cases, anxiety disorders (17.8%), panic attacks (10.8%), alcohol use disorder (1.6%), schizophrenia (1.6%), bipolar disorder (1.3%), eating disorder (0.6%) and impulse control disorders (0.3%). As far as clinical variables were concerned, the mean age at onset was 31.74 ± 15.79 years, while the mean age at first referral was 35.28 ± 15.73 years. Most patients referred to either a psychiatrist (35.7%), a CAPU (2.9%) or a psychotherapy unit (22.3%), even though contact with other health services (emergency department, GP or other specialists) was also common (38.9%). More than half of the subjects suffered from comorbid psychiatric conditions, namely, in decreasing order: personality disorders (23,2%), other anxiety disorders (4.1%), MDD (3.8%), alcohol or susbtance use disorder (3.2%), post-traumatic stress disorder (PTSD, 1.3%), eating disorder (1%), somatization disorders

(0.6%), bipolar disorder (0.3%), adjustment disorder (0.3%), obsessive-compulsive disorder (0.3%), and gambling disorder (0.3%). In detail, as regards personality disorders, 14% suffered from a cluster C disorder, 8.9% from a cluster B and 1.4% from a cluster A disorder, while 9.6% suffered from multiple and 0.6% from unspecified personality disorders. Lifetime alcohol or substance use disorders were reported by 6.4% of the participants.

In terms of clinical presentation, almost two thirds (71.3%) of patients predominantly experienced unexpected panic attacks. Nocturnal panic attacks were prevalent in a small fraction of the subjects (10.8%), while agoraphobia was reported by 61.5% of the participants. With respect to pharmacological treatment, the vast majority of patients had been prescribed with BDZs, either alone (31.2%) or in combination with SSRIs (29.3%), 11.2% only received treatment with antidepressants (either SSRI [9.6%] or TCA [0.3%] monotherapy or the combination of both [1.3%]), while the remainder (28.3%) were not taking any medication.

The mean DUI-SSRI of the total sample was 64.25 ± 112.74 months, while the mean DUI-BDZ was significantly shorter (35.09 ± 78.62; W= 6216, p<0.0001) (Figure 1) [Insert Figure 1]. In addition, with regard to the DUI-SSRI, there were significant differences in comparison with previous results from Altamura et al., 2010[28]: mean DUI = 44.35 months (SD ±59.86, N=96); and Dell'Osso et al., 2013[9]: mean DUI = 39.55 months (SD ±57.25, N=138), while not differing significantly from findings reported by Benatti et al., 2016[27]: mean DUI= 53.9 months (SD ±81.5, N=49) (respectively: t=2.256, p=0.024; t=3.082, p=0.002; t=0,780, p=0,438) (Figure 2) [Insert Figure 2].

Discussion

We sought to explore and compare latency to different pharmacological treatments (SSRIs vs BDZs) in a sample of 314 Italian outpatients affected by PD.

In accordance with the literature [4,37], PD patients were mostly women, showing a male to female ratio of almost 1:2. In addition, around two thirds of participants had a family history of psychiatric disorder, with an almost 15% rate of familiality for PD or panic attacks. With respect to age at onset, the mean value observed in the sample was approximately 32 years, which is consistent with previous findings [9,28] confirming a common onset of PD in early adulthood. Interestingly, age at first referral was slightly older (around 35 years). This result is also consistent with previous reports[9] and highlights how panic symptoms are still underrecognized and, consequently, under-treated. More than one-third of patients had contacted health care services outside the mental health field (emergency room, GP or other specialists), which might contribute to a delay in proper diagnosis and treatment. Moreover, PD is frequently comorbid with medical illnesses, whose symptoms often overlap and complicate its diagnostic recognition [38]. Our results confirmed this association, with one-fifth of patients presenting physical comorbidities. Although a frequent association with MDD, dysthymia, BD, other anxiety disorders and personality disorders has been reported, with at least one lifetime comorbid condition in up to 80% of PD patients [4,5,39], in our sample, around 50% of patients had a comorbid psychiatric disorder, MDD, BD and other anxiety disorders being less prevalent than previously reported. In terms of prevalence of personality disorders, 35.7% of our patients met DSM-IV criteria for at least one personality disorder, a result that slightly differs from earlier studies reporting possible comorbidity rates between 40 and 65% [40–42]. The most represented personality disorders belonged to the C cluster (14%), confirming the well established link between PD and anxious personality traits [43,44]. Coexistence of multiple personality disorders was not uncommon (almost 10% of the sample). Although co-occurrence of panic and alcohol and substance use disorders (SUD) is of frequent observation in PD patients [45–49], with an estimated prevalence of any SUD above 20% [5], our findings showed lower lifetime prevalence rates, with only 6.4% of participants meeting DSM-5 criteria for SUD. This result needs to be cautiously interpreted

and might be partly explained by potential reporting bias and the frequent unavailability of relatives or external referents and records from outpatient substance abuse services, with possible underestimation of such comorbidity pattern.

More than two-thirds of participants reported the predominance of unexpected panic attacks, though only around 10% experienced nocturnal attacks regularly, a slightly lower value than previously documented [50]. A possible explanation may be that all participants were receiving CBT and some were taking medications that might have reduced their occurrence. In line with previous observations [42], agoraphobia was diagnosed in approximately 60% of participants.

As far as treatment is concerned, the gold standard first-line treatment for PD according to major international guidelines comprises either SSRIs or the SNRI venlafaxine and/or non-pharmacological interventions such as cognitive-behavioral psychotherapy (CBT) [30,31,37,51]. Tricyclic antidepressants (TCAs) have also been found efficacious in PD, but are not recommended as first-line treatment due to safety and tolerability issues [35]. BDZs may be useful for acute anxiety or agitation or while waiting for the onset of the efficacy of antidepressants [30,31,37,51]: longer-term use of these compounds, however, is not recommended because of the potential risk of abuse, sedation, cognitive impairment, and psychomotor alterations [51,52], even though some research supports their use in comparison to antidepressants [53], likely in patients with specific characteristics. In fact, BDZs are not effective for the treatment of conditions that are often comorbid with PD, such as MDD or OCD [37]. In the present sample, we analyzed the current pharmacological treatment rate and found that approximately one-third of patients was not taking any medication, while more than two-thirds were receiving BDZ treatment, either as monotherapy or in conjunction with SSRIs. Only around 10% of the sample was taking antidepressants alone. These results highlight the discrepancy

between recommendations from international treatment guidelines and routine clinical practice, and are consistent with previous findings reported in the literature [5].

We documented a mean latency to first guideline-recommend PD treatment of more than 5 years. As already mentioned, a growing body of literature has investigated DUI in patients affected by PD [9,25–28], reporting values ranging between 3-5 years. The acute onset of PD, its symptoms having a great impact on individual functioning, the presence of physical symptomatology and different degrees of insight might be expected to bring affected individuals to seek professional help earlier than patients with other mental disorders - around 60% of patients with PD reported contact with health care services because of panic symptoms at least once [6] and around 30% have contact within one year of the onset [54]. Nevertheless, the condition remains often under-recognized, as our report seems to confirm. Although the majority of individuals with PD without agoraphobia, and nearly 90% of those with PD and agoraphobia are recognized by their GPs as having a psychiatric disorder [6], only a minority receives proper treatments, with a negative impact on outcome and response to treatment [3,11,55]. In this respect, we detected a mean latency to the first BDZ prescription of approximately 3 years. In addition, when we compared DUI-SSRI versus DUI-BDZ, we observed a statistically significant difference (of approximately two and a half years) between these two measurements. This finding indicates that, in spite of guideline recommendations, BDZs continue to be widely prescribed as first treatment in PD [29], even though existing evidence suggests that long-term BDZ prescription might delay proper treatment in patients with mood and anxiety disorders, including PD [56,57].

Finally, we compared latency to SSRI treatment with findings from previous studies and observed some significant differences. The longer DUI in the present study could reflect a longer latency to treatment in PD patients, but may be influenced by the setting of our study: all participants were

undergoing CBT treatment, and may have been more inclined to access a non-pharmacological intervention. Nonetheless, this result further confirms the substantial delay in the administration of an adequate pharmacological treatment in PD patients, stressing the need for early diagnosis and treatment in order to achieve a better clinical outcome.

In the interpretation of the results, the following limitations need to be considered. First, the naturalistic way of collecting data relied on recall by patients and available family members, who may not have always been precise. Second, our findings are related to treatment-seeking patients so may not be representative of the wider population of individuals with PD. Third, local mental health service delivery factors and cultural attitudes may have influenced patients' access, diagnosis, and treatment. Finally, all participants were receiving CBT, which is considered among first-line treatment options for PD according to international guidelines [30,31,37,51]. In this perspective, it would be interesting to compare latency to CBT and/or other psychotherapy treatments versus latency to pharmacological treatment, and to examine their potential interactions.

Conclusion

The present study reported a significant difference between DUI-BDZ and DUI-SSRI in PD patients and a longer DUI-SSRI than previously observed. Such results might be of relevance with regard to clinical outcome and overall prognosis in PD patients. Further and longitudinal analyses in larger samples are needed to confirm or refute reported findings and provide additional insight into the factors influencing DUI and its relationship with clinical course, outcome and morbidity of PD.

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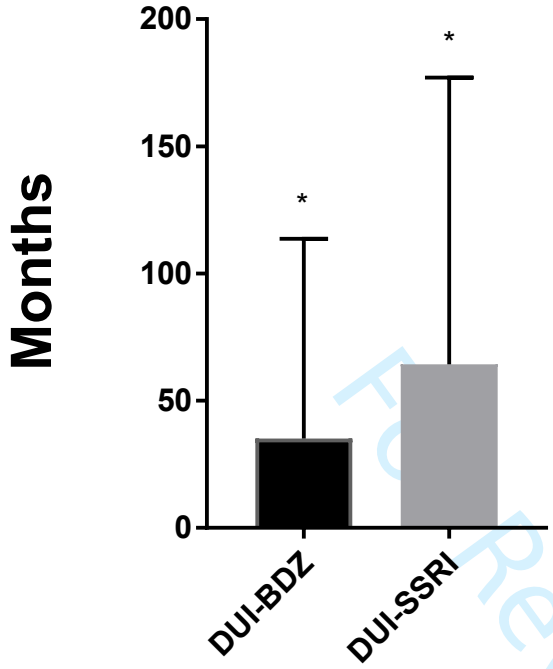
Table 1: Socio-demographic and clinical variables of the total sample

Variables		Total sample (N=314)
Gender	Female	66.6%
	Male	33.4%
Age (years)		42.55 ± 16.11
Education	Elementary	2.5%
	Middle school	38.9%
	High school	40.1%
	University	18.5%
Relationship status	Single	52.5%
	In a relationship	47.5%
Work	Student	18.5%
	Employed	54.8%
	Unemployed	16.9%
	Retired	9.9%
Age at onset (years)		31.74 ± 15.79
Age at first referral (years)		35.28 ± 15.73
Type of first referral	CAPU	2.9%
	ER	4.1%
	GP	18.2%
	Psychiatry	35.7%
	Psychotherapy Unit	22.3%
	Other specialist	16.6%
Psychiatric family history	No	35.7%
	Yes	64.3%
Family history of panic disorder or attacks	No	85.7%
	Yes	14.3%
Physical comorbidity	No	79.6%
	Yes	20.4%
Psychiatric comorbidity	No	48.1%
	Yes	51.9%
Psychiatric comorbidity (type)	Personality disorder	23.2%
	Anxiety disorder (other)	4.1%
	MDD	3.8%
	Alcohol or substance use disorder	3.2%
	PTSD	1.3%
	Eating disorder	1.0%
	Somatization disorder	0.6%
	Bipolar disorder	0.3%
	Adjustment disorder	0.3%
	Obsessive-compulsive disorder	0.3%
	Gambling disorder	0.3%
Personality disorder (type)	Cluster A	1.4%
	Cluster B	8.9%
	Cluster C	14.0%
	Multiple PDs	9.6%
	PD-NOS	0.6%
	None	64.3%
Lifetime alcohol or substance use disorder	No	93.6%
	Yes	6.4%
DUI- BDZ (months)		35.09 ± 78.62
DUI - SSRI (months)		64.25 ± 112.74
Pharmacological therapy (current)	BDZ monotherapy	31.2%
	SSRI monotherapy	9.6%
	SSRI+BDZ	29.3%
	SSRI+TCA	1.3%
	TCA	0.3%
	None	28.3%
Type of panic attack (prevalent)	Situational	28.7%
	Spontaneous	71.3%
Nocturnal panic attacks (prevalent)	No	89.2%
	Yes	10.8%
Agoraphobia	No	38.5%
	Yes	61.5%

Values for categorical and continuous variables are expressed as mean ±SD.

Abbreviations: ER= emergency room; GP= general practitioner; CAPU= child and adolescent psychiatric unit; MDD= major depressive disorder; PTSD= post-traumatic stress disorder; NOS= not otherwise specified; DUI= duration of untreated illness; BDZ= benzodiazepines; SSRI= selective serotonin reuptake inhibitors.

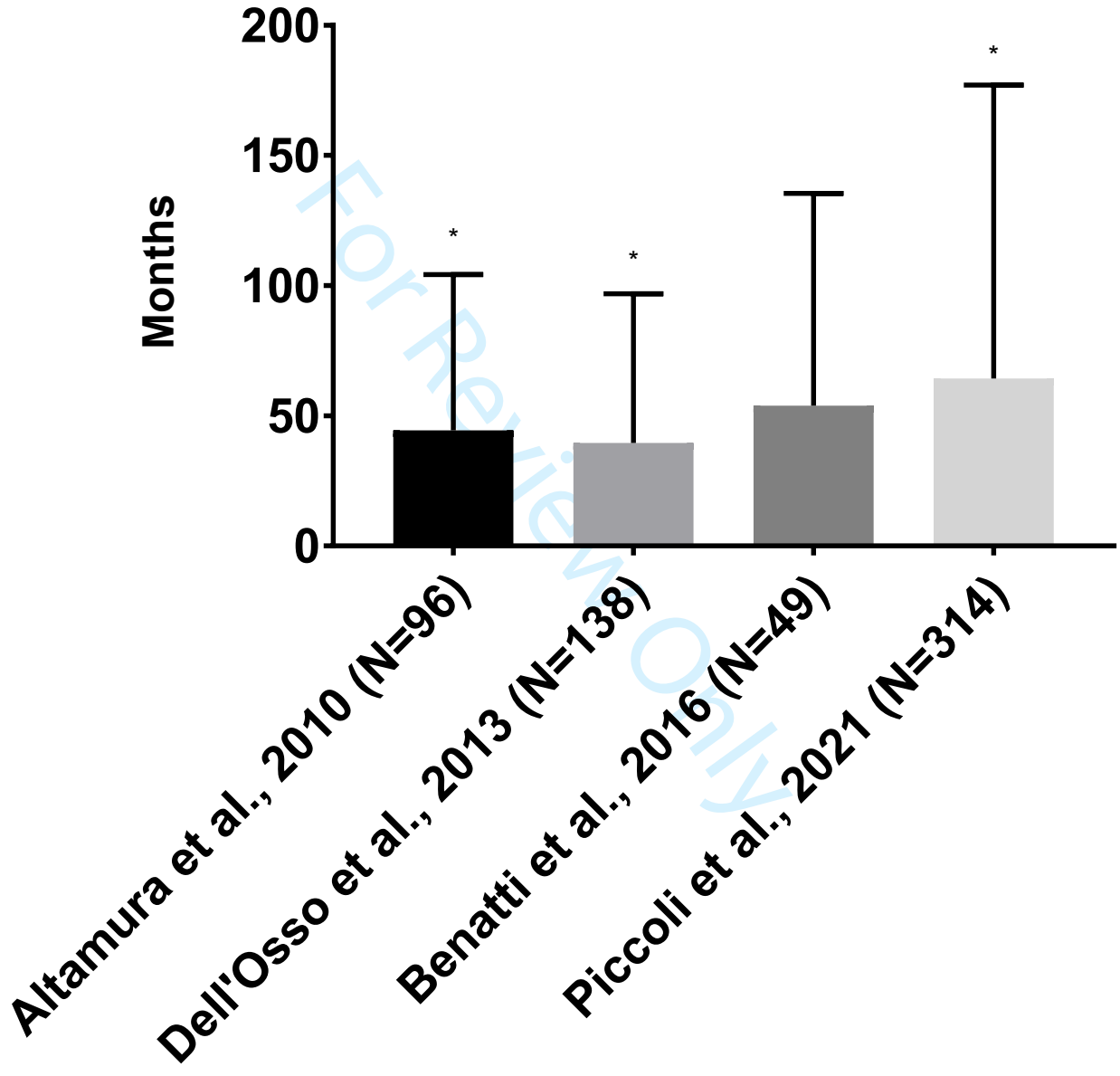
Figure 1: Latency to different pharmacological treatments (DUI-BDZ *vs* DUI-SSRI) in patients with Panic Disorder



P<0.05;

Abbreviations: DUI: duration of untreated illness; BDZ: benzodiazepines; SSRI: selective serotonin reuptake inhibitors.

Figure 2: Differences in terms of DUI-SSRI (expressed in months) in patients with Panic Disorder between the present study and previous reports investigating latency to pharmacological treatments



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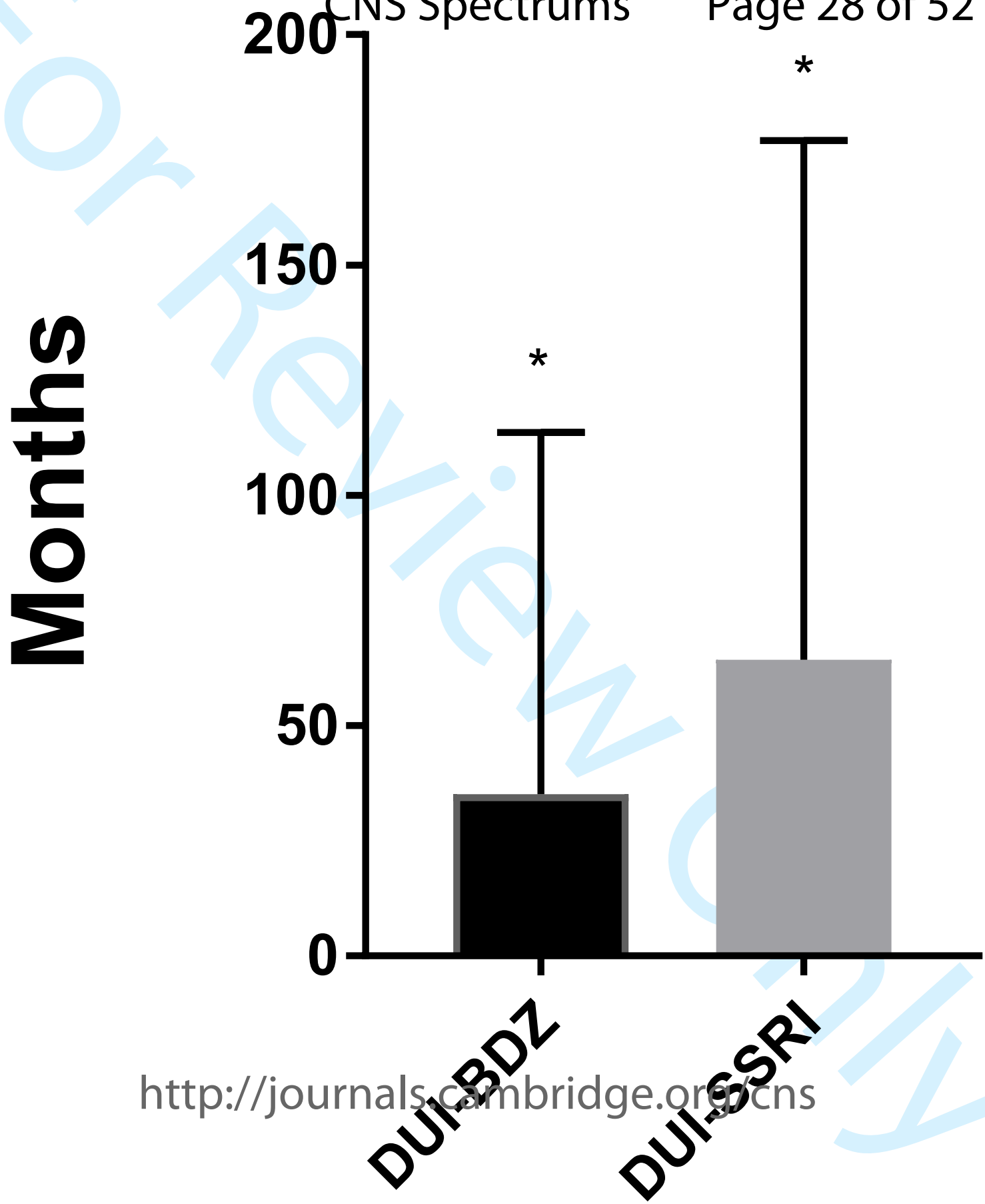

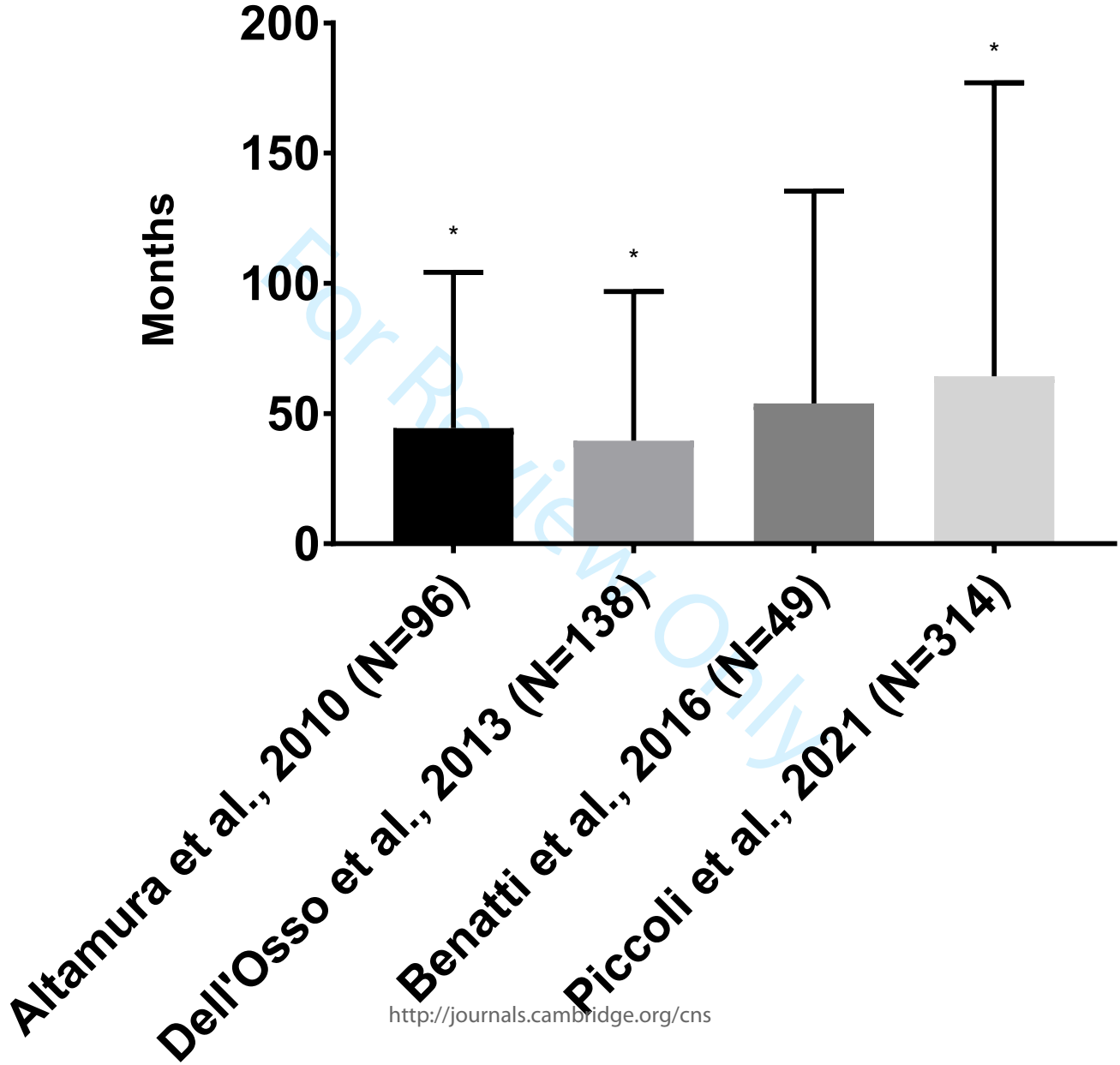

Original research

Latency to selective serotonin reuptake inhibitor versus benzodiazepine treatment in patients with Panic Disorder: a naturalistic study

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Keywords: psychopharmacology, panic disorder, anxiety disorders, duration of untreated illness, treatment

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Figures: 2

Abstract

Introduction: Panic disorder (PD) is a prevalent and impairing anxiety disorder with previous reports suggesting that the longer the condition remains untreated, the greater the likelihood of non-response. However, PD patients may wait for years before receiving a guideline- recommended pharmacological treatment. The widespread prescription of benzodiazepines (BDZ) for managing anxiety symptoms and disorders might delay the administration of pharmacotherapy according to guidelines (e.g.: selective serotonin reuptake inhibitors, SSRIs). The present study aimed to determine the mean duration of untreated illness (DUI) in a sample of PD patients, to quantify and compare DUI-SSRI to DUI-BDZ, and to compare findings with those from previous investigations.

Materials and methods: 314 patients with a DSM-5 diagnosis of PD were recruited from an Italian outpatient psychotherapy unit, and epidemiological and clinical variables were retrieved from medical records. Descriptive statistical analyses were undertaken for sociodemographic and clinical variables, Wilcoxon matched-pair signed rank test was applied to compare the distribution of DUI-SSRI *vs*. DUI-BDZ, and Welch's t-test was performed to compare findings with those from previous studies.

Results: The mean DUI-SSRI of the total sample was 64.25 ± 112.74 months, while the mean DUI-BDZ was significantly shorter (35.09 ± 78.62 months; $p<0.0001$). A significantly longer DUI-SSRI, compared to findings from previous studies, was also observed.

Conclusion: The present results confirm a substantial delay in implementing adequate pharmacological treatments in PD patients, and highlight the discrepancy between

recommendations from international treatment guidelines and common clinical practice in relation to BDZ prescription.

Introduction

Panic disorder (PD) is typically a long-lasting condition, characterized by recurrent unexpected panic attacks, persistent worry about experiencing future attacks and their consequences and/or subsequent maladaptive changes in behavior [1]. It affects 1.6%-2.2% of the world population [2,3], with a lifetime prevalence of 1.5-5% [4] and a 12-month prevalence between 1.8-2.7% [5,6]. Previous investigations suggest that the longer PD remains untreated, the greater the likelihood of non-response [3]. Therefore, the duration of untreated illness (DUI), defined as the interval between the onset of a specific psychiatric disorder and the administration of the first appropriate pharmacological treatment according to guidelines in compliant subjects [7–9] may be a potential predictor of clinical course and outcome [10,11].

To date, DUI has been investigated across different psychiatric conditions, including major depressive disorder (MDD) [12–15], bipolar disorder [16], obsessive-compulsive disorder (OCD) [17–19], somatization [20], eating [21] and schizophrenia spectrum disorders [8,22–24]. In respect to anxiety disorders, previous reports indicate a significantly shorter DUI compared to findings from studies conducted with patients with obsessive-compulsive, mood, and schizophrenia spectrum disorders [9,25,26]. Moreover, differences in terms of latency to treatment emerged between patients with PD and generalized anxiety disorder (GAD), with PD patients having a shorter DUI [9,27]. Indeed, patients with PD may wait for years before receiving an adequate pharmacological treatment, with possible negative prognostic implications, such as a higher risk of developing comorbid MDD [11,13].

Nonetheless, only a few studies have assessed DUI in PD. A preliminary naturalistic study in a sample of 96 subjects attending an Italian outpatient clinic found a mean DUI of almost four years [28], while a more recent investigation involving a larger sample (n=138) showed a DUI of slightly more than 3 years [9]. Finally, a 4-5 years DUI was reported in an Italian multicenter study conducted on a sample

of 49 patients with PD[27]. Previous research has some methodological limitations, such as relatively small sample sizes, and the lack of assessment of potentially important variables related to psychopathological onset and latency to treatment, including type of first referral, presence of comorbidities and clinical presentation.

Focusing on pharmacological treatments of anxiety disorders and PD in particular, the widespread prescription of benzodiazepines (BDZ) as monotherapy might delay the initiation of guideline-recommended long-term treatments [29]. Treatment guidelines support the efficacy of selective serotonin reuptake inhibitors (SSRIs) or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine as first line pharmacological treatment of PD, and recommend caution for BDZ prescription due to associated risks of abuse, tolerance and withdrawal [30,31]. As little is known about the assessment and comparison between DUI-SSRI and DUI-BDZ in patients affected by PD, we sought to determine the mean DUI and related variables in a large sample of PD patients, with the additional aim of comparing findings with those from previous investigations in the field.

Methods

Study sample

A total of 314 patients with PD, who attended the outpatient psychotherapy unit of the Psychiatric Department of the Ospedale L. Sacco of Milan, Italy, between January 2015 and March 2019, was recruited. Data was retrospectively collected from patients' medical records. Patients had been diagnosed according to DSM-5 criteria by means of the Structured Clinical Interview for DSM-5 (SCID) [32] at the time of the first contact with the service. Subjects primarily affected by schizophrenia-spectrum disorders, unipolar or bipolar mood disorders, somatization, obsessive-compulsive and post-traumatic spectrum disorders, mild/major neurocognitive disorders and

anxiety disorders secondary to substance use or other medical conditions were excluded from the study. Comorbidity with personality disorders was allowed and assessed via the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) [33], administered by psychologists with specific training. Patients were interviewed after providing written informed consent for participation in the study and for having their clinical records examined for research purposes.

Assessment

Demographic and clinical variables collected during clinical interviews with patients (and, when available, relatives) were retrieved from medical records, including gender, age, education, age at onset, medical comorbidities, lifetime substance and alcohol abuse, age at first contact with psychiatric services, type of service at first contact (i.e., emergency department, psychotherapy unit, child and adolescent psychiatry unit [CAPU], general practitioner [GP], psychiatrist or other clinician), age at first pharmacological treatment, current pharmacological treatment, family history of psychiatric disorders and presence of agoraphobia or nocturnal panic attacks and prevalent type of panic attacks. As previously proposed [7,8,34], DUI-SSRI was defined as the interval (in months) between the onset of the disorder and the administration of the first adequate pharmacological treatment (i.e. SSRI), at an appropriate dosage and for an adequate period of time, in compliant patients, in agreement with international treatment guidelines[35,36]. Furthermore, DUI-BDZ, indicating the interval (in months) between PD onset and administration of benzodiazepines, was also calculated.

Statistical analysis

Descriptive analyses were carried out for sociodemographic and clinical variables of the total sample. Because of the non-Gaussian data distribution (assessed with the Shapiro-Wilk test), a nonparametric test (Wilcoxon matched-pair signed rank test) was applied to compare the distributions of DUI-SSRI *versus* DUI-BDZ. Welch's t-test was performed to compare results with findings from previous studies conducted by our group in independent samples. The level of significance was set at 0.05. Statistical analyses were performed using SPSS for Windows software (version 20; SPSS Inc., Chicago, Illinois, USA) and Prism (GraphPad Prism version 9.0).

Results

The main sociodemographic and clinical variables of the sample are summarized in Table 1 [Insert Table 1]. Male to female ratio was about 1:2, with a mean age of 42.55 ± 16.11 years. Of the 314 participants, 202 (64.3%) had a positive psychiatric family history, specifically for MDD in the 19.4% of cases, anxiety disorders (17.8%), panic attacks (10.8%), alcohol use disorder (1.6%), schizophrenia (1.6%), bipolar disorder (1.3%), eating disorder (0.6%) and impulse control disorders (0.3%). As far as clinical variables were concerned, the mean age at onset was 31.74 ± 15.79 years, while the mean age at first referral was 35.28 ± 15.73 years. Most patients referred to either a psychiatrist (35.7%), a CAPU (2.9%) or a psychotherapy unit (22.3%), even though contact with other health services (emergency department, GP or other specialists) was also common (38.9%). More than half of the subjects suffered from comorbid psychiatric conditions, namely, in decreasing order: personality disorders (23,2%), other anxiety disorders (4.1%), MDD (3.8%), alcohol or susbtance use disorder (3.2%), post-traumatic stress disorder (PTSD, 1.3%), eating disorder (1%), somatization disorders

(0.6%), bipolar disorder (0.3%), adjustment disorder (0.3%), obsessive-compulsive disorder (0.3%), and gambling disorder (0.3%). In detail, as regards personality disorders, 14% suffered from a cluster C disorder, 8.9% from a cluster B and 1.4% from a cluster A disorder, while 9.6% suffered from multiple and 0.6% from unspecified personality disorders. Lifetime alcohol or substance use disorders were reported by 6.4% of the participants.

In terms of clinical presentation, almost two thirds (71.3%) of patients predominantly experienced unexpected panic attacks. Nocturnal panic attacks were prevalent in a small fraction of the subjects (10.8%), while agoraphobia was reported by 61.5% of the participants. With respect to pharmacological treatment, the vast majority of patients had been prescribed with BDZs, either alone (31.2%) or in combination with SSRIs (29.3%), 11.2% only received treatment with antidepressants (either SSRI [9.6%] or TCA [0.3%] monotherapy or the combination of both [1.3%]), while the remainder (28.3%) were not taking any medication.

The mean DUI-SSRI of the total sample was 64.25 ± 112.74 months, while the mean DUI-BDZ was significantly shorter (35.09 ± 78.62; W= 6216, p<0.0001) (Figure 1) [Insert Figure 1]. In addition, with regard to the DUI-SSRI, there were significant differences in comparison with previous results from Altamura et al., 2010[28]: mean DUI = 44.35 months (SD ±59.86, N=96); and Dell'Osso et al., 2013[9]: mean DUI = 39.55 months (SD ±57.25, N=138), while not differing significantly from findings reported by Benatti et al., 2016[27]: mean DUI= 53.9 months (SD ±81.5, N=49) (respectively: t=2.256, p=0.024; t=3.082, p=0.002; t=0,780, p=0,438) (Figure 2) [Insert Figure 2].

Discussion

We sought to explore and compare latency to different pharmacological treatments (SSRIs vs BDZs) in a sample of 314 Italian outpatients affected by PD.

In accordance with the literature [4,37], PD patients were mostly women, showing a male to female ratio of almost 1:2. In addition, around two thirds of participants had a family history of psychiatric disorder, with an almost 15% rate of familiality for PD or panic attacks. With respect to age at onset, the mean value observed in the sample was approximately 32 years, which is consistent with previous findings [9,28] confirming a common onset of PD in early adulthood. Interestingly, age at first referral was slightly older (around 35 years). This result is also consistent with previous reports[9] and highlights how panic symptoms are still underrecognized and, consequently, under-treated. More than one-third of patients had contacted health care services outside the mental health field (emergency room, GP or other specialists), which might contribute to a delay in proper diagnosis and treatment. Moreover, PD is frequently comorbid with medical illnesses, whose symptoms often overlap and complicate its diagnostic recognition [38]. Our results confirmed this association, with one-fifth of patients presenting physical comorbidities. Although a frequent association with MDD, dysthymia, BD, other anxiety disorders and personality disorders has been reported, with at least one lifetime comorbid condition in up to 80% of PD patients [4,5,39], in our sample, around 50% of patients had a comorbid psychiatric disorder, MDD, BD and other anxiety disorders being less prevalent than previously reported. In terms of prevalence of personality disorders, 35.7% of our patients met DSM-IV criteria for at least one personality disorder, a result that slightly differs from earlier studies reporting possible comorbidity rates between 40 and 65% [40–42]. The most represented personality disorders belonged to the C cluster (14%), confirming the well established link between PD and anxious personality traits [43,44]. Coexistence of multiple personality disorders was not uncommon (almost 10% of the sample). Although co-occurrence of panic and alcohol and substance use disorders (SUD) is of frequent observation in PD patients [45–49], with an estimated prevalence of any SUD above 20% [5], our findings showed lower lifetime prevalence rates, with only 6.4% of participants meeting DSM-5 criteria for SUD. This result needs to be cautiously interpreted

and might be partly explained by potential reporting bias and the frequent unavailability of relatives or external referents and records from outpatient substance abuse services, with possible underestimation of such comorbidity pattern.

More than two-thirds of participants reported the predominance of unexpected panic attacks, though only around 10% experienced nocturnal attacks regularly, a slightly lower value than previously documented [50]. A possible explanation may be that all participants were receiving CBT and some were taking medications that might have reduced their occurrence. In line with previous observations [42], agoraphobia was diagnosed in approximately 60% of participants.

As far as treatment is concerned, the gold standard first-line treatment for PD according to major international guidelines comprises either SSRIs or the SNRI venlafaxine and/or non-pharmacological interventions such as cognitive-behavioral psychotherapy (CBT) [30,31,37,51]. Tricyclic antidepressants (TCAs) have also been found efficacious in PD, but are not recommended as first-line treatment due to safety and tolerability issues [35]. BDZs may be useful for acute anxiety or agitation or while waiting for the onset of the efficacy of antidepressants [30,31,37,51]: longer-term use of these compounds, however, is not recommended because of the potential risk of abuse, sedation, cognitive impairment, and psychomotor alterations [51,52], even though some research supports their use in comparison to antidepressants [53], likely in patients with specific characteristics. In fact, BDZs are not effective for the treatment of conditions that are often comorbid with PD, such as MDD or OCD [37]. In the present sample, we analyzed the current pharmacological treatment rate and found that approximately one-third of patients was not taking any medication, while more than two-thirds were receiving BDZ treatment, either as monotherapy or in conjunction with SSRIs. Only around 10% of the sample was taking antidepressants alone. These results highlight the discrepancy

between recommendations from international treatment guidelines and routine clinical practice, and are consistent with previous findings reported in the literature [5].

We documented a mean latency to first guideline-recommend PD treatment of more than 5 years. As already mentioned, a growing body of literature has investigated DUI in patients affected by PD [9,25–28], reporting values ranging between 3-5 years. The acute onset of PD, its symptoms having a great impact on individual functioning, the presence of physical symptomatology and different degrees of insight might be expected to bring affected individuals to seek professional help earlier than patients with other mental disorders - around 60% of patients with PD reported contact with health care services because of panic symptoms at least once [6] and around 30% have contact within one year of the onset [54]. Nevertheless, the condition remains often under-recognized, as our report seems to confirm. Although the majority of individuals with PD without agoraphobia, and nearly 90% of those with PD and agoraphobia are recognized by their GPs as having a psychiatric disorder [6], only a minority receives proper treatments, with a negative impact on outcome and response to treatment [3,11,55]. In this respect, we detected a mean latency to the first BDZ prescription of approximately 3 years. In addition, when we compared DUI-SSRI versus DUI-BDZ, we observed a statistically significant difference (of approximately two and a half years) between these two measurements. This finding indicates that, in spite of guideline recommendations, BDZs continue to be widely prescribed as first treatment in PD [29], even though existing evidence suggests that long-term BDZ prescription might delay proper treatment in patients with mood and anxiety disorders, including PD [56,57].

Finally, we compared latency to SSRI treatment with findings from previous studies and observed some significant differences. The longer DUI in the present study could reflect a longer latency to treatment in PD patients, but may be influenced by the setting of our study: all participants were

undergoing CBT treatment, and may have been more inclined to access a non-pharmacological intervention. Nonetheless, this result further confirms the substantial delay in the administration of an adequate pharmacological treatment in PD patients, stressing the need for early diagnosis and treatment in order to achieve a better clinical outcome.

In the interpretation of the results, the following limitations need to be considered. First, the naturalistic way of collecting data relied on recall by patients and available family members, who may not have always been precise. Second, our findings are related to treatment-seeking patients so may not be representative of the wider population of individuals with PD. Third, local mental health service delivery factors and cultural attitudes may have influenced patients' access, diagnosis, and treatment. Finally, all participants were receiving CBT, which is considered among first-line treatment options for PD according to international guidelines [30,31,37,51]. In this perspective, it would be interesting to compare latency to CBT and/or other psychotherapy treatments versus latency to pharmacological treatment, and to examine their potential interactions.

Conclusion

The present study reported a significant difference between DUI-BDZ and DUI-SSRI in PD patients and a longer DUI-SSRI than previously observed. Such results might be of relevance with regard to clinical outcome and overall prognosis in PD patients. Further and longitudinal analyses in larger samples are needed to confirm or refute reported findings and provide additional insight into the factors influencing DUI and its relationship with clinical course, outcome and morbidity of PD.

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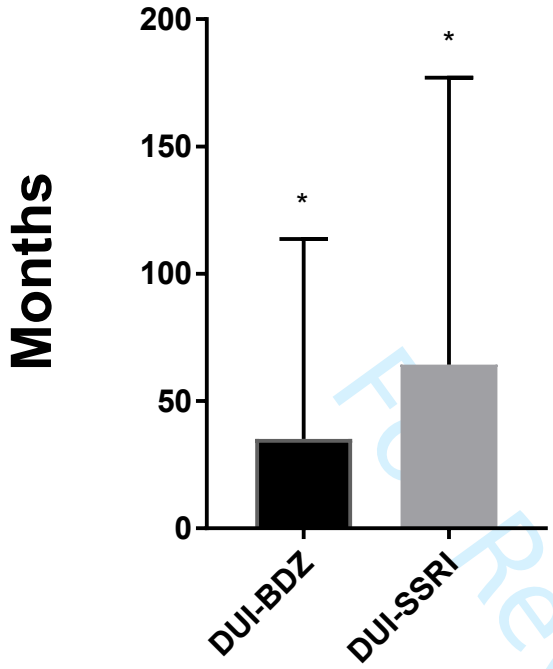
Table 1: Socio-demographic and clinical variables of the total sample

Variables		Total sample (N=314)
Gender	Female	66.6%
	Male	33.4%
Age (years)		42.55 ± 16.11
Education	Elementary	2.5%
	Middle school	38.9%
	High school	40.1%
	University	18.5%
Relationship status	Single	52.5%
	In a relationship	47.5%
Work	Student	18.5%
	Employed	54.8%
	Unemployed	16.9%
	Retired	9.9%
Age at onset (years)		31.74 ± 15.79
Age at first referral (years)		35.28 ± 15.73
Type of first referral	CAPU	2.9%
	ER	4.1%
	GP	18.2%
	Psychiatry	35.7%
	Psychotherapy Unit	22.3%
	Other specialist	16.6%
Psychiatric family history	No	35.7%
	Yes	64.3%
Family history of panic disorder or attacks	No	85.7%
	Yes	14.3%
Physical comorbidity	No	79.6%
	Yes	20.4%
Psychiatric comorbidity	No	48.1%
	Yes	51.9%
Psychiatric comorbidity (type)	Personality disorder	23.2%
	Anxiety disorder (other)	4.1%
	MDD	3.8%
	Alcohol or substance use disorder	3.2%
	PTSD	1.3%
	Eating disorder	1.0%
	Somatization disorder	0.6%
	Bipolar disorder	0.3%
	Adjustment disorder	0.3%
	Obsessive-compulsive disorder	0.3%
	Gambling disorder	0.3%
Personality disorder (type)	Cluster A	1.4%
	Cluster B	8.9%
	Cluster C	14.0%
	Multiple PDs	9.6%
	PD-NOS	0.6%
	None	64.3%
Lifetime alcohol or substance use disorder	No	93.6%
	Yes	6.4%
DUI- BDZ (months)		35.09 ± 78.62
DUI - SSRI (months)		64.25 ± 112.74
Pharmacological therapy (current)	BDZ monotherapy	31.2%
	SSRI monotherapy	9.6%
	SSRI+BDZ	29.3%
	SSRI+TCA	1.3%
	TCA	0.3%
	None	28.3%
Type of panic attack (prevalent)	Situational	28.7%
	Spontaneous	71.3%
Nocturnal panic attacks (prevalent)	No	89.2%
	Yes	10.8%
Agoraphobia	No	38.5%
	Yes	61.5%

Values for categorical and continuous variables are expressed as mean ±SD.

Abbreviations: ER= emergency room; GP= general practitioner; CAPU= child and adolescent psychiatric unit; MDD= major depressive disorder; PTSD= post-traumatic stress disorder; NOS= not otherwise specified; DUI= duration of untreated illness; BDZ= benzodiazepines; SSRI= selective serotonin reuptake inhibitors.

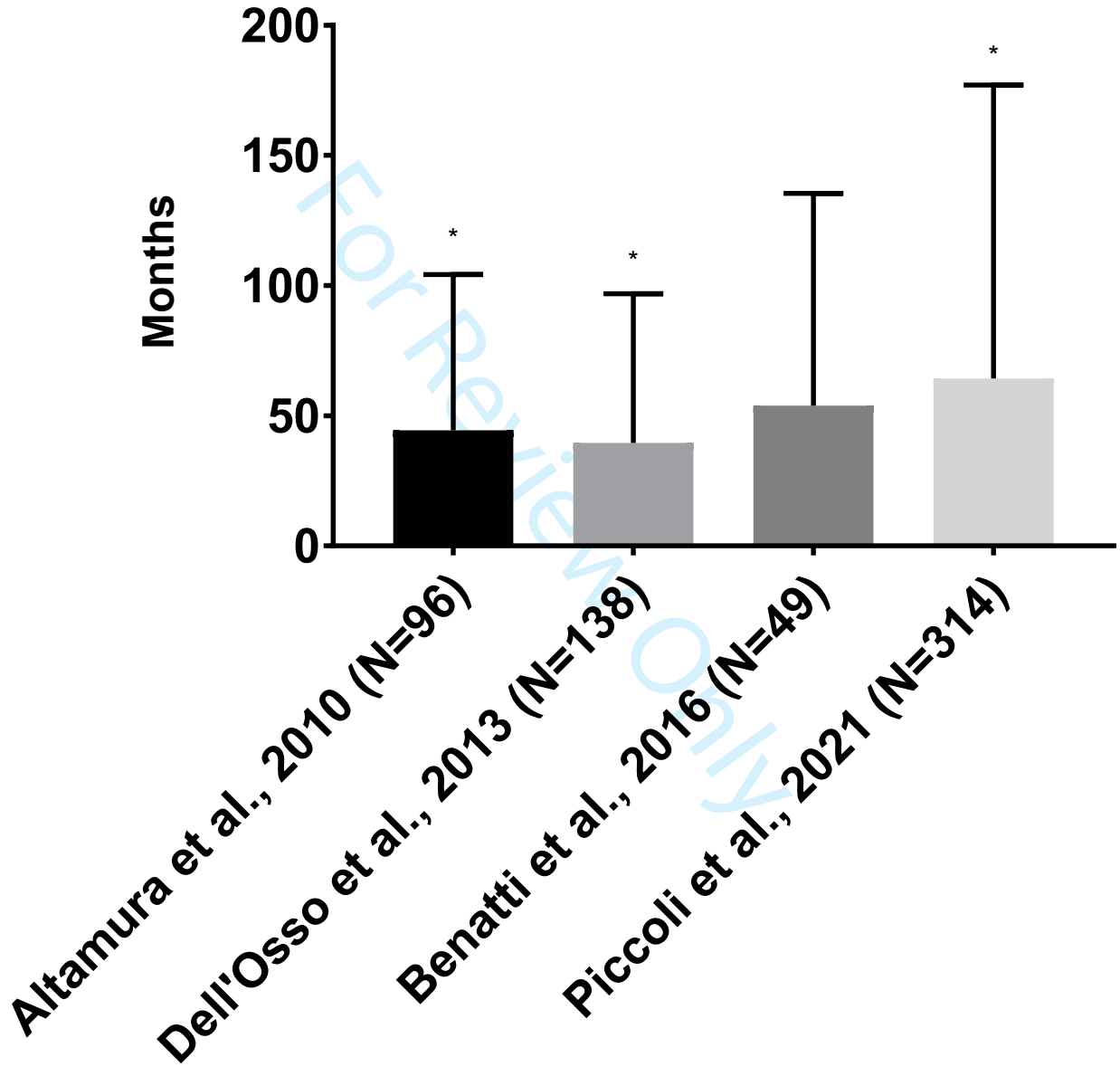
Figure 1: Latency to different pharmacological treatments (DUI-BDZ *vs* DUI-SSRI) in patients with Panic Disorder



P<0.05;

Abbreviations: DUI: duration of untreated illness; BDZ: benzodiazepines; SSRI: selective serotonin reuptake inhibitors.

Figure 2: Differences in terms of DUI-SSRI (expressed in months) in patients with Panic Disorder between the present study and previous reports investigating latency to pharmacological treatments



P<0.05;

Abbreviations: DUI: duration of untreated illness; SSRI: selective serotonin reuptake inhibitors