First Benzodiazepine prescription, determinants and related effects over duration of untreated illness in patients with Psychotic and Affective Disorders

Running Head: benzodiazepines and latency to non-symptomatic treatment

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ABSTRACT

It is established that delayed effective pharmacotherapy plays a significant role in the overall burden of psychiatric disorders. Often, such conditions are treated with symptomatic drugs, i.e. benzodiazepines (BZDs), in relation to their rapid onset of action and safety, despite long-term side effects.

Our aims were to assess the influence of treatment with BZDs on the duration of untreated illness (DUI) and whether specific socio-demographic and clinical factors could influence the choice of BZD as first treatment in 545 patients affected by Schizophrenia, Mood and Anxiety spectrum disorders.

Statistical analyses (One-way ANOVA and $\chi 2$) were performed to compare patients who used BZDs as first treatment (BZD w/) and those who did not (BZD w/o).

The overall DUI, regardless to diagnosis, resulted significantly longer in BZD w/ patients, who also experienced more frequently anxious/depressive symptoms at onset. Furthermore, BZDs w/ patients more frequently had first therapist contact following a personal decision (more frequently with psychologists or general practitioners) and experimented more frequently phobias, than BZDs w/o ones.

Present findings suggest that BZDs may lengthen the overall DUI and that their prescription seems to be influenced by specific socio-demographic and clinical factors. Further studies are needed to confirm present findings.

Keywords: benzodiazepines, duration of untreated illness, mood disorders, psychotic disorders, anxiety disorders

INTRODUCTION

Mental disorders are highly prevalent and disabling conditions, estimated to contribute to the 5.4% of Disability-Adjusted Life Years (DALYs) and 17.4 % of global Years Lived with Disability (YLDs) (Charara et al., 2017). There is a univocal consensus about the burden of mental disorders on patients' quality of life and global functioning and, in many cases, on related caregivers' (Wagner et al., 2006). Indeed, psychiatric disorders often remain underdiagnosed and not adequately treated as a consequence of many factors including also social stigma and lack of mental health literacy (Wei et al., 2017).

All the mentioned factors may contribute to extend the overall duration of untreated illness (DUI), and to worsen the prognosis and response to psychopharmacological treatment in specific subgroups of patients.

With respect to DUI, even though different definitions exist in literature (Breitborde et al., 2009), it is mainly defined as the time elapsing from the onset of a psychiatric disorder and the subsequent administration of the first pharmacological treatment at standard dosages, for an adequate period of time in a compliant patient, according to treatment guidelines (Dell'Osso & Altamura, 2010). Several mental illnesses, such as schizophrenia spectrum disorders (Barnes et al., 2000; Buoli et al., 2013; Marshall et al., 2005; McGlashan, 1999; Penttilä et al., 2010; Perkins et al., 2005), depressive disorders (Dell'Osso & Altamura, 2010), anxiety disorders (Altamura et al., 2008; Altamura et al., 2005; Ghio et al., 2014) and obsessive compulsive disorder (Dell'Osso et al., 2015) have been investigated in relation to DUI, underlying its predictive role in treatment outcome and the importance of early intervention to prevent long-term disability (Dell'Osso & Altamura, 2010).

BDZs represent one of the largest and most widely prescribed classes of psychotropic

drugs, particularly at the onset of several psychiatric disorders (Dell'Osso & Lader, 2013). According to guidelines recommendations, anxiety and affective disorders, sleep disorders, alcohol withdrawal, delirium and aggressive behavior in psychoses seem to represent the clinical conditions of more frequent use for BZDs (Ashok, 2006; Bandelow et al., 2008; Kennedy et al., 2009; Dell'Osso et al., 2013).

More in detail, in psychiatric clinical practice, mental disorders, especially at onset, might be underestimated and often initially treated exclusively with symptomatic drugs, BZDs (Dell'Osso et al., 2016). BDZs, in fact, present rapid onset of action and safety profile, but also have considerable short and long-term side effects. Indeed, BZDs can induce dose-dependent tolerability problems, like sedation, fatigue, lethargy, drowsiness, hangover and rebound symptoms after interruption, cognitive symptoms, development of dependence, hypotonia and ataxia (Buffett-Jerrott & Stewart, 2002; Koyama et al., 2013; Lader et al., 2009; Pariente et al., 2009). Moreover a higher risk of dementia was found among long-term users of BZDs, especially for long acting compounds (Billioti de Gage et al., 2014; Shash et al., 2016). Another understated aspect is BZDs treatment during breastfeeding, since Post-Partum Depression represents a prevalent disorder and sedating drugs could cause infant's central nervous system depression (Chow & Koren, 2015).

In relation to BZDs use and specific psychiatric diagnosis, patients with Major Depression and Anxiety Disorders have been observed to report massive use of BZDs as first treatment, compared with patients with Schizophrenia spectrum disorders (Dell'Osso et al., 2015).

The present study primarily aimed to evaluate the influence of treatment with benzodiazepines (BZDs) on the DUI, representing the latter compounds a fast relief of

symptoms that might delay the first prescription of an adequate and clinically approved pharmacological treatment. The secondary aim was to assess whether specific socio-demographic or clinical factors could influence the choice of BZDs as first treatment in patients affected by Schizophrenia, Mood and Anxiety spectrum disorders. We hypothesized that results might help to better characterize specific clinical features in psychiatric disorders in order to identify patients that have a higher risk of BZD misuse and of remaining untreated.

METHODS

Sample

Study sample consisted of 545 consecutive patients (both outpatients and inpatients), attending three major psychiatric services in the North and south of Italy: (a) Department of Mental Health of the Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico of Milan, (b) Department of Psychiatry of Ospedale San Gerardo, Monza Brianza, and (c) Department of Public Health, Section of Psychiatry and Psychiatric Clinic of Cagliari. Patients signed a written informed consent to participate to the study and they underwent a clinical interview, in order to assess their psychiatric diagnosis and complete the questionnaire. Moreover, their clinical records were used for research purpose. Patients were required to have one of the following diagnoses, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSMIV-TR) (APA, 1994): Major Depressive Disorder (MDD), Bipolar Disorder (BD), Generalized Anxiety Disorder (GAD), Panic Disorder (PD), Obsessive Compulsive Disorder (OCD), Adjustment Disorders, Delusional Disorder, and Schizophrenia. Diagnoses were made through the

Structured Clinical Interview for DSM-IV Axis I disorders (First et al., 2002), administered by psychiatrists with specific training. In case of comorbid disorder, the disorder assessed in relation to the psychopathological onset and DUI had to be the one causing the most significant discomfort to the patient, the greatest impact on quality of life, and representing the main motivation for help-seeking.

Assessment

Socio-demographic and clinical variables, collected during clinical interviews, were: sex, age, age at onset, age at first diagnosis, age at first pharmacological treatment, first pharmacological treatment, family history for psychiatric disorders, occurrence of onset-related stressful events, use of benzodiazepines as first treatment, first therapist referral (psychiatrist, psychologist, neurologist or other clinician), help-seeking decision (autonomous or driven by others) and first therapy setting (outpatient or inpatient). In particular, patients underwent a clinical interview guided by the administration of the psychopathological onset and latency to treatment questionnaire (POLT-Q), a recently developed tool aimed to specifically assess factors characterizing access and latency to first pharmacological treatment in patients suffering from psychiatric disorders. The questionnaire includes a preliminary part, collecting patient sociodemographic features, and two sections respectively focused on psychopathological onset (Section 1) and first pharmacological treatment (Section 2). POLT-Q is a brief, clinician administrated questionnaire that was found to be easy to administer by clinicians and well-accepted by patients (Dell'Osso et al., 2017). As conventionally accepted (Dell'Osso et al., 2013; Dell'Osso & Altamura, 2010), the DUI was defined as the time interval – in months – elapsing between the onset of the disorder and the administration of the first

pharmacological treatment, in compliant subjects, at appropriate dosage and for an adequate period of time, in agreement with recently updated International treatment guidelines (Bauer et al., 2013; Grunze et al., 2013).

Statistical analysis

Descriptive analyses were performed on the total sample. Study sample was then divided in two subgroups, according to the use of BZDs as first treatment. One-way ANOVA for continuous variables and $\chi 2$ test for dichotomous ones were performed for comparison between patients who used BZDs as first treatment (BZD w/) and those who did not (BZD w/o). The level of significance for all statistical analyses was set at 0.05.

RESULTS

Socio- demographic and clinical variables of the whole sample (n = 545) are summarized in Table 1. The sample showed a similar gender distribution (male 52.8% and females 47.2%) and a mean age of 48,1 ±14.3 years. The mean DUI of the total sample resulted to be 59.7±100.3 months.

The comparison between the two subgroups showed different statistically significant results, reported in Table 2.

In particular, the DUI resulted significantly longer in BZD w/ vs BZD w/o patients (72.9 ± 105.9 vs 53.1 ± 96.9 months; $p < 0.05$), as shown in Figure 1. Moreover, BZDs w/ subjects reported more frequently anxious/depressive symptoms at onset (31% VS 21%, $p < 0.01$), and less frequentely psychotic symptoms (12% vs 62%, $p < 0.01$), compared to BZD w/o ones.

BZD w/ patients resulted to be affected more often by Major Depression Disorder (MDD)

and Adjustment Disorders (respectively: 43% vs 32%; 9% vs 3%), while BZD w/o ones by Bipolar Disorder (BD), Obsessive Compulsive Disorder (OCD) and Schizophrenia spectrum disorders (respectively: 18% vs 10%; 9% vs 3%; 11% vs 4%; $p < 0.0001$).

Furthermore, BZDs w/ patients more frequently reported an autonomous help-seeking decision (48% vs 36%, $p < 0.01$), while BZDs w/o subjects had first visit encouraged by relatives or friends (62% vs 47%, $p < 0.01$). BZDs w/ patients were found to contact more frequently psychologists or general practitioners (GPs) rather than psychiatrists as first therapists compared to BZD w/o ones (respectively: 21% vs 9%; 47% vs 27%; 24% vs 55%; $p < 0.0001$).

Finally, BZDs w/ subjects experienced more frequently phobia in comorbidity, than BZDs w/o ones (24% vs 16%, $p < 0.05$).

The remaining investigated socio-demographic and clinical features did not show any significant difference between the two subgroups.

DISCUSSION

In the present study, we sought to assess whether patients suffering from various psychiatric disorders had different latency to BDZs, compared to approved treatments for their conditions. BDZs, in fact, represent symptomatic drugs (Stahl, 2016), useful for a fast relief of symptoms, which may lengthen the overall first psychiatric referral and the administration of the first adequate psychopharmacological treatment. BZD w/ patients were found to experience a significantly longer DUI than BZD w/o ones. Moreover, the statistical analysis showed a significant association between BZDs w/ subjects and the presence of anxious/depressive symptoms at onset of illness, compared to psychotic

manifestations.

Previous studies from our group reported that patients with anxiety disorders, particularly GAD, more frequently received BDZs as first therapy (Benatti et al., 2016). The relevant correlation between BZDs w/ subjects and the presence of anxious/depressive symptoms at onset of illness may be explained in light of the tendency of anxious disorders to manifest in an insidious way (Roy-Byrne & Wagner, 2004). On the other hand, patients suffering from psychotic spectrum disorders, which usually present an acute onset (APA, 2013), more frequently reported a first psychiatric referral, due to a more severe clinical presentation and more frequent hospital admission at onset (Dell'Osso et al., 2015).

Another relevant result of the present study is that BZDs w/ patients were found to contact more frequently psychologists or general practitioners (GPs), rather than psychiatrists, as first therapists, compared to BZD w/o ones. Previous studies reported that patients with an anxiety disorder often contact their GP rather than a psychiatrist (Dell'Osso et al., 2015) and BDZs are frequently prescribed by GPs as initial treatments for anxiety (Baldwin et al., 2012; Dell'osso & Lader, 2013), even though treatment guidelines recommend the use of second generation antidepressants (Baldwin et al., 2014; Starcevic, 2014).

Many recent studies focused on BZDs prescription patterns, underlying, in particular, how these compounds are widely administered and frequently misused and suggesting the importance to reduce inappropriate BZDs use, improving evidence-based practice and prescription's monitoring across different countries. More in detail, a Norwegian study of primary care reviewed 3452 prescriptions for BZDs prescribed by GPs over 2 months (Straand & Rokstad, 1997). Of these, over half were prescribed to patients older than 65 years, showing BDZs are extensively prescribed by GPs in patients affected by different

psychiatric conditions, especially mood and anxiety disorders, also including the elderly population. The broad BDZs prescription has been shown not only in the Norwegian population (Tvete et al., 2015), but elsewhere as well. For instance, BZD harmful misuse has been pointed out by different studies in Canada, (Murphy et al., 2016), USA (Bachhuber et al., 2016), France (Rosman et al., 2011) and UK (Davies et al., 2017). All these studies converged about the need to recognize BZDs misuse as a serious public health problem and highlighted the need of a specific intervention in order to reduce BDZ inappropriate prescriptions.

In this perspective, it is crucial not only to educate the population about BDZ misuse but also to involve the GPs, heading towards a more appropriate prescription of these compounds, considering their side effects (Albrecht et al., 2014) and the risk of delaying the initiation of a more appropriate pharmacological treatment as pointed out by the results of present study. Indeed, while BZDs can initially be helpful in relieving acute psychiatric symptoms, they carry the risk of dependence and withdrawal (Bandelow et al., 2008). In addition, their long-term use has been associated with impaired cognitive attention (Petursson et al., 1983) and verbal memory (Barker et al., 2004), dementia (Billioti de Gage et al., 2014) and major risk of car accidents (Smink et al., 2010), hip fractures (Wagner et al., 2004), and falls, particularly in the elderly (Bartlett et al., 2009).

The tendency to contact to GPs rather than psychiatrist for the assessment of psychiatric symptoms and to take symptomatic compounds might be influenced by the stigma towards psychiatric disorders and psychotropic drugs, leading patients to hesitate to choose psychiatrists as first therapists. Del Vecchio and colleagues showed that, among health professionals, GPs resulted to be the most frequently chosen by patients with a first episode

of psychosis, mainly because of stigma and wrong attribution of psychiatric symptoms. These reasons were correlated with help-seeking delay too (Del Vecchio et al., 2015). Moreover, even when relatives recognize the need for a psychiatric help for the patient, they prefer to avoid psychiatric referral (Franz et al., 2010; Gerlinger et al., 2013; Griffiths et al., 2014; Windell & Norman, 2013) and more often address to GPs or other 'less stigmatizing' health professionals (Falloon, 2000; Skeate et al., 2002; Tait et al., 2005). According to the literature, stigma affects not only psychotic disorders, but all mental illnesses, including depression and anxiety (Jorm & Reavley, 2013), and has an impact on DUI and psychiatric referral. Furthermore, the high levels of stigma towards psychiatric disorders (Fiorillo et al., 2011; Magliano et al., 2003) and the limited availability of specific services for early intervention in many countries (Cocchi et al., 2013; Pingani et al., 2014; Pollice et al., 2012) may represent an important barrier to the psychiatric care of patients in the early phases of the disorder.

Focusing on these considerations, it should be useful to work in two different but complementary directions. First of all, mental health literacy needs to be improved (Jorm, 2000). Psychiatric patients often do not receive an appropriate treatment for many years and must be trained in order to recognize prodromic symptoms, which must be evaluated by a psychiatrist, and to avoid symptomatic compounds misuse.

Secondly, GPs could play a key role in limiting BZDs misuse, abuse or dependence, as shown in a recent report highlighting the active involvement of GPs, particularly for educating their patients to cease or reduce BZD use, in order to decrease BZD consumption (Darker et al., 2015).

Even though our sample resulted to be quite representative, the following methodological

limitations should be pointed out to interpret the aforementioned findings. Since the POLT-Q retrospectively collected socio-demographic and clinical variables, the presence of recall bias cannot be excluded, particularly for patients with most remote onset and for elderly people. Nonetheless, as already mentioned, all clinical data from the POLT-Q were cross-checked with family members/caregivers and previous medical charts, when available. Moreover, the recruitment of patients coming from different catchment areas may have reflected local differences in terms of efficiency of psychiatric services as well as different socio-cultural attitudes, which, in turn, may have influenced reported results.

In conclusion, specific diagnostic and clinical factors, such as onset symptoms, first diagnosis, personal decision to contact the first therapist, phobia in comorbidity and first referral, seem to condition BZD use as first treatment at the onset of different psychiatric disorders. In clinical practice, early detection is important to reduce the DUI, which reflect the latency to approved and evidence based treatments and could be delayed by inappropriate BZD use. Further studies are needed to raise awareness of BZD misuse and better identify patients deserving non symptomatic treatment. Raising health literacy and psychiatric disease awareness might be useful to let GPs, clinicians, patients and the general population recognize prodromic symptoms and consequently activate the most appropriate pathways of care when necessary.

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