The Burden of Agoraphobia in Worsening Quality of Life in a Community Survey in Italy

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Objective Current nosology redefined agoraphobia as an autonomous diagnosis distinct from panic disorder. We investigated the lifetime prevalence of agoraphobia, its association with other mental disorders, and its impact on the health-related quality of life (HR-QoL).

Methods Community survey in 2,338 randomly selected adult subjects. Participants were interviewed with the Advanced Neuropsychiatric Tools and Assessment Schedule (ANTAS), administered by clinicians. The diagnoses were based on the ICD-10 criteria. The Short-Form Health Survey (SF-12) was used to quantify HR-QoL.

Results In the sample, 35 subjects met the criteria for agoraphobia (1.5%), with greater prevalence among women (2.0%) than men (0.9%): odds ratio (OR) 2.23; 95% CI: 1.0-5–2. Agoraphobia was more often seen among those with (n=26; 1.1%) than without (n=9; 0.4%) panic disorder: OR=8.3; 2.9–24.4. Co-morbidity with other mental disorders was substantial. The mean score of SF-12 in people with agoraphobia was 35.2±7.8, with similar levels of HR-QoL in people with (35.3±7.9) or without (34.8±7.3) panic disorder: ANOVA: F(1;33)=0.0; p=1.00.

Conclusion One out of seventy people may suffer from agoraphobia in their lifetime. The attributable burden in terms of HR-QoL is substantial and comparable to the one observed for chronic mental disorders such as major depression, post-traumatic stress disorder, or obsessive-compulsive disorder.   **Psychiatry Investig**

Key Words Agoraphobia, Panic disorder, Major depressive disorder, Quality of life, Community survey, Epidemiology.

INTRODUCTION

Agoraphobia is usually defined as a state of anxiety that develops when someone is in public or crowded places and thinks s/he cannot receive appropriate help when in need or cannot escape from when facing danger. Thus, people with agoraphobia strive to avoid such places or situations and tend to develop intense anxiety when forced to do it. Until Diagnostic and

Statistical Manual of mental disorders-fourth edition (DSM-IV), agoraphobia was a qualifier of panic disorder.[1] However, in the fifth revision of the diagnostic and statistical manual of the America Psychiatric Association, so-called DSM-5, agoraphobia was granted a formal diagnosis, which can occur independently from any other anxiety disorder.[2] The current definition of agoraphobia in DSM-5 assigns a prominent role in the diagnosis to marked fear or anxiety about actual or anticipated exposure to public places or situations such as "using public transportation; being in open spaces; being in enclosed places; standing in line or being in a crowd; or being outside of the home alone in other situations" (DSM-5 code: 300.22).[2] Fear or anxiety must recur most of the time in at least two or more of the listed common situations. For the diagnosis, the individual must show both fears of exposure to public places and active avoidance of such situations. The fear or anxiety must not be related to a realistic threat or be explained by sociocultural context, and it should be not a consequence of substance use or withdrawal from it. Six months or more of persistent or recurrent symptomatology must be proved to make the diagnosis. On an epidemiological ground, the first age of diagnosis is relatively early: mid to late twenties. No specific "cause" has been identified for the onset of agoraphobia, but a set of risk factors tends to recur in the history of those who had received the diagnosis: besides genetic predisposition, the experience of grief or bereavement early in life, adverse or traumatic events during childhood, and parental overprotectiveness are the most often cited. A history of childhood fears or night terrors is a frequent antecedent of agoraphobia in youths and adults.[3] The estimated lifetime prevalence is around 1.3% and the incidence rate is 0.9% with no difference between men and women.[4] There is no established treatment for agoraphobia. For mild forms of the disorder, cognitive-behavioral therapy (CBT) is thought to be effective in alleviating symptoms and improving quality of life.[5] For more severe variants, antidepressants are considered the first line of intervention.[6]

Agoraphobia is currently separated from panic disorder.[4,7] The new category has made it possible to better define a non-negligible share of people with agoraphobia without the panic disorder in the general population and to start defining agoraphobia as a disorder per se with a great impact on the well-being of the individual regardless of the presence of the concomitance or not of panic disorder.[4] However, even in the DSM-5 era, there are no tools validated with these criteria in literature, and many studies of validation in languages other than English still are based on interviews that adopt the DSM-IV system.[8,9] The still-evolving long work of developing new diagnostic tools has not yet reached a point to allow the conduct of community surveys with the new criteria.

The definition of agoraphobia in the tenth edition of the World Health Organization's International Classification of Diseases (ICD-10), closely resembles the definition of the disorder of the DSM-5 (ICD-10 code: F40.0),[10] albeit lacking the temporal restriction of six-month continuous active symptoms. Thus, it could be helpful to re-analyze the records of databases of community studies already carried out using the ICD-10 system for the diagnosis of anxiety disorders.

This study aimed at investigating the prevalence, the demographic profile and the impact on the quality of life (QoL) of agoraphobia diagnosed according to the criteria of the ICD-10 in a large and representative sample of the general population of Italy.

METHODS

The study was approved by the by the ethical committee of the Italian National Health Institute (Rome) on August 21th, 2010 and complied with the provisions of the Declaration of Helsinki of 1995 and its revisions.[11] All participants signed a written informed consent.

Design, participants and procedure

The data were drawn for the databank of a community survey.[12] The study was aimed at evaluating appropriateness of drug prescription for the treatment of mental disorders in Italy, especially bipolar disorder, with a focus on antidepressants. The sample was randomly selected from the records of at least three municipalities (one urban, one suburban, and at least one rural) of six Italian regions. Those regions were selected as representative of the geographic and economic characteristics of the whole set of Italian regions. Randomization was performed in eight cells obtained after stratification of the sample by gender and age (four strata 18−24; 25−44; 45−64; >64). Invitation in the study was by contact with the relevant general practitioners, who were initially asked to participate in the study and convey the invitation to their patients for survey collaboration. Thereafter, researchers contacted the participants by phone call and mail. Trained physicians or clinical psychologists carried out the interviews, face to face in the subjects' homes. After the explanation of the finalities of the study and the aqcquisition of a written informeed consent, interviewers asked the interviewees to show them their drug boxes, if any, and were provided with a folder to retain all of the psychotropic drug box covers. Participants were then interviewed with a semi-structured interview and were requested to fill in some self-report questionnaires, including the Health Related (HR)-QoL Survey Short Form. Whenever during the interview the participants had revealed symptoms related to a mental disorder under investigation, they received an appropriate referral to primary (general practitioner) or tertiary care (local psychi-

atric services). A detailed methodology description had ben already published earlier.[12]

Tools

1) The psychiatric interviews were conducted by means of Advanced Tools and Neuropsychiatric Assessment Schedule -Structured Clinical Interview (ANTAS).[12] It is a semi-structured, full computerized interview derived in part from the SCID.[13] ANTAS allows diagnosis of mood, anxiety and eating disorders according to DSM-IV-TR and ICD-10 with high reliability and cross-validity with SCID.[12]

2) The Health Related (HR)-QoL Survey Short Form (SF-12)[14] was used to assess perceived H-R-QoL as a measure of the impact of agoraphobia and the comorbid psychiatric conditions The SF-12 allows to measure: physical health and functionning, emotional condition, pain, general health status, vitality, social funtiionning and mental wellbeing. The HR-QoL, as measured by the SF-12, is a construct that measures the status and outcome of chronic diseases not only about the symptoms but also the relevant components of daily life.[15]

Definitions and subgroups

The diagnosis of major depressive disorder, post-traumatic stress disorders and anxiety disorders were defined according to ICD-10 criteria.[10] All diagnoses were estimated as lifetime prevalence.

Statistical analysis

The odds ratio (OR) (univariate analysis) for ICD-10 agoraphobia diagnosis and age, gender and comorbidity with ICD-10 diagnosed disorders, was calculated using as a "pivot" one group by table. The χ^2 test was used for measuring statistical significance. Miettinen's simplified method was used for calculating Odds ratios and 95% confidence intervals.[16] The SF-12 scores by groups were compared by ANOVA one-way statistic.

The burden on the impairing HR-QoL "attributable" to agoraphobia (attributable burden) was defined as the difference between HR-QoL (mean score on the SF-12) in the sample of people without agoraphobia and HR-QoL of people with agoraphobia (as mean score of SF-12) drawn from the community survey database. The control sample was obtained by randomization after blocks. For each person with agoraphobia, a cell selecting all the people without agoraphobia of the same age was carried out, thus four people were selected by randomization from each obtained cell.

The burden in worsening of HR-QoL attributable to agoraphobia was also compared to a similar meaure obtained to other diseases, in previous case-control studies that have adopted the same database as sources of controls.

In people with agoraphobia the number of those who sub-mitted an SF-12 questionnaire score on quality of life below 35 (poor HR-Qol) and above 38 (good HR-Qol) was also calculated; these cutt offs were suggested by the distribution of the score to the scale in the general population.[17]

RESULTS

The overall lifetime prevalence of agoraphobia was of 35 cases out of 2338 people (1.5%). There were 26 cases with comorbid panic disorder and 9 cases without comorbid panic disorder.

Table 1 showed lifetime prevalence of agoraphobia by sex and age, the prevalence was 0.9% in men 2.0% in women (OR= 2.23; 95% CI: 1.0−5.2), no differences were found according to age distribution.

The cases of agoraphobia with panic disorder have higher lifetime prevalence than those without panic disorder (1.1% vs. 0.4% OR=8.3; 2.9−24.4) (Table 2), with no differences in distribution by gender and age in the subgroups of agoraphobia (with and without panic disorder), with a marginal rise among young people (OR=8.0; 0.9−73.4).

Table 3 showed the association between agoraphobia and other anxiety disorders, major depressive disorder, and post-traumatic stress disorder. Agoraphobia was often comorbid with major depressive disorder (OR=16.2; 7.3−35.6); panic disorder (OR=87.0; 37.3−208.2); simple phobia OR=7.7 (2.5−21.9); social phobia OR=59.3 (12.6−271.3); generalized anxiety disorder (OR=12.0; 4.5−30.6); obsessive-compulsive disorder (OR=7.1; 2.0−22.5); post-traumatic stress disorder (OR= 9.2; 1.4−44.9).

The co-morbidity with anxiety disorders, major depression and post-traumatic stress disorder was perfectly superimposable in cases of agoraphobia with or without panic disorder (Table 4).

Table 1. Lifetime prevalence of agoraphobia by gender and age

	N (%)	χ^2 (df=1)	p	OR	95% CI
<25 males	0 (0)	-			
25−44	2 (0.5)	0.001*	0.977	0.0	0−11.7
45−64	3 (1.0)	0.250*	0.617	0.0	0−5.2
>64	4 (2.1)	0.403*	0.235	0.0	0−2.14
Total males*	9 (0.9)				
<25 females	3 (2.2)	-			
25−44	9 (2.0)	0.226	0.884	1.01	0.29−3.72
45−64	13 (2.7)	0.214	0.643	0.77	0.21−2.47
>64	1 (0.4)	0.242	0.875	0.91	0.22−3.34
Total females†	26 (2.0)	5.520	0.033	2.24	1.0−5.17
<45 vs. >44 in M+F	1.3	0.734	0.392	0.74	0.4−1.4

*with Yates's correction, †female vs. males

The mean score of SF-12 in people with agoraphobia was 35.2±7.8, with similar levels of HR-QoL in people with (n=26) or without panic disorder (n=9): 35.3±7.9 vs. 34.8±7.3 [ANOVA: F(1;33)=0.0; p=1.00]. As many as 14 out of 35 individuals diagnosed with agoraphobia (40%) had an SF-12 score higher than or equal to 39, which indicates a good level of HR-QoL, while 16 (45.7%) had an HR-QoL level lower than 35 (poor HR-QoL). Overall, agoraphobia showed an attributable burden comparable to that observed for the other investigated disorders (Table 5).

Table 2. Comparing lifetime prevalence by gender and sex of agoraphobia with panic disorder vs agoraphobia without panic disorder

	Agoraphobia with panic disorder (%)	Agoraphobia without panic disorder (%)	χ^2 (df=1)	p	OR	95% CI
Males	5 (0.5)	4 (0.4)	0.294*	0.192	0.3	0.06−1.5
Female	21 (1.6)	5 (0.4)				
<45 with vs. without	13 (1.2)	1 (0.1)	0.097*	0.056	8.0	0.9−73.4
>44 with vs. without	13 (1.0)	8 (0.6)				
Total (1.5%)	26 (1.1)	9 (0.4)	14.63*	<0.0001	8.3	2.9−24.4

*with Yates's correction

Table 3. Comorbidity between agoraphobia and other disorders

	Comorbid with agoraphobia (%)	χ^2 (df=1)	p	OR	95% CI
Major depressive disorder	12 (34.3)	96.63	<0.0001	16.2	7.3−35.6
Panic disorder	26 (74.2)	425.3	<0.0001	87.0	37.3−208.2
Simple phobia	5 (14.3)	17.51*	<0.0001	7.7	2.5−21.9
Social phobia	4 (11.4)	86.66*	<0.0001	59.3	12.6−271.3
Generalized anxiety disorder	7 (20.0)	47.3	<0.0001	12.0	4.5−30.6
Obsessive-compulsive disorder	4 (11.4)	12.27*	<0.0001	7.1	2.0−22.5
Post-traumatic stress disorder	2 (5.7)	6.23*	0.0013	9.2	1.4−44.9

*with Yates's correction

Table 4. Comorbidity in agoraphobia with and without panic disorders

	Agoraphobia with panic disorder (%)	Agoraphobia without panic disorder (%)	Fisher' p	OR	95% CI
Major depressive disorder	10 (47.6)	2 (22.2)	1.00	3.2	0.5−19.0
Simple phobia	4 (10.0)	1 (11.1)	1.00	1.8	0.2−19.9
Social phobia	3 (14.2)	1 (11.1)	1.00	1.3	0.1−14.9
Generalized anxiety disorder	5 (23.8)	2 (22.2)	1.00	1.1	0.2−7.1
Obsessive-compulsive disorder	3 (14.2)	1 (11.1)	1.00	1.3	0.1−14.9
Post-traumatic stress disorder	2 (5.7)	0 (0)	1.00	-	-

Table 5. Attributable Burden in worsening Quality of Life due to Agoraphobia and comparison with other disorders

	SF-12 (mean±SD)	Attributable burden due to the disorder	ANOVA*
Agoraphobia	35.2±7.8	3.4±3.6 (N=35)	
Major depressive disorder	33.8±9.2	5.6±3.6 (N=37)	F(1;70)=6.6; p=0.012
Panic disorder	35.5±4.6	2.9±0.9 (N=123)	F(1;156)=0.72; p=0.396
Simple phobia	35.8±6.1	2.5±2.4 (N=54)	F(1;87)=2.48; p=0.119
Obsessive-compulsive disorder	35.4±6.9	2.9±6.0 (N=88)	F(1;121)=0.21; p=0.646
Post-traumatic stress disorder	36.3±6.1	3.9±1.0 (N=26)	F(1;59)=0.47; p=0.495

Attributable Burden=Quality of Life in a matching control group without Agoraphobia (matching controls 1/4 from the community). *comparison with agoraphobia without panic disorder. SD: standard deviation, N: number (i.e., sample size), SF-12: 12-item Short-Form Health Survey, ANOVA: analysis of variance

DISCUSSION

The lifetime prevalence of agoraphobia found by our study is in the range of the estimates found by studies that used DSM-IV criteria for diagnosis or that have recalculated rates with DSM-5. The World Health Survey (WHS) found lifetime prevalence of agoraphobia of 1.4% according to DSM-IV criteria and 1.5% according with those of DSM-5.[4] The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) had found in the US a lifetime prevalence of 1.3% (as a sum of panic disorder with agoraphobia and agoraphobia without panic disorder).[18] In the same year and still in the US, the National Comorbidity Survey Replication (NCS-R) had found a lifetime prevalence of panic disorder with agoraphobia of 1.1% and agoraphobia with panic disorder 0.8% according DSM-IV.[19]

The prevalence of agoraphobia without panic disorder in the present study is in the range of previous studies conducted with the DSM-5: from 0.2% of NESARC to 1.0% of WHS. It is also not far from the results of a study carried out in Derry, North Irleand,[20] which used a two phases design and found a lifetime prevalence of 0.7% of ICD-10 agoraphobia without panic disorder. As far as the specific prevalence of agoraphobia without panic disorder is concerned, our studies seem to be quite distant from almost all studies conducted using DSM-IV as a criterion and highly structured tools for diagnosis conducted by lay interviewers.[21] However, in the European Study on the Epidemiology of Mental Disorders (ESEMeD) ther pooled data from France, Belgium, Spain, The Netherland and Italy showed a liferime prevalence of agoraphobia without panic disorder of 0.9%.[22]

Other studies found a higher prevalence than in the present study: Munchen Region, Germany (2.6%);[23] Finland (0.7%);[24] Dresden, Germany (1.8%);[25] The Netherland (1.6%);[26] Oslo Norway (3.1%);[27] Germany (2%).[28] It should be noted, however, that the only study that used trained clinical interviewers (in Sesto Fiorentino, Italy), even with structured interviews and using DSM-IV as a criterion, lifetime prevalence figures were much lower than in the others DSM-IV surveys (0.4% versus, on average, 2.0%) and much closer to ours.[29] In the WHS database, the comparison between the diagnoses of agoraphobia without panic disorder carried out applying DSM-IV and DSM-5 criteria indicated that these two systems tend to identify different conditions under the same diagnosis.[4] Conversely, the diagnoses that are done according to the criteria of the ICD-10 are closer to the ones that are based on the criteria of the DSM-5.[4] It should be borne in mind that the WHS study, lay interviewers applied a highly structured interview while in the present study clinicians used semi-structured interviews. It is therefore possible that the more clinically oriented method of this study has allowed a more accurate identifi-

cation of even the light forms of panic disorder (thus decreasing the quote of agoraphobia without panic disorder). In the past, the debate on the reproducibility of the diagnoses conducted with the semi-structured interviews was in fact the subject of a heated debate, especially regarding mood disorders, with irreconciliable point of views.[30,31]

The two subgroups of agoraphobia with and without panic disorder found in the present study show a very similar profile in terms of age and gender distribution, comorbidity with anxiety disorders, post-traumatic stress disorder, and major depressive disorder, as well as of the level of impairment of quality of life. These findings support the notion that agoraphobia is a homogeneous group and not the confluence of two separate conditions.

As far as the level of impairment due to agoraphobia is concerned, the result can be considered partly unexpected. Agoraphobia is often thought to be a disabling disorder.[32] However, in this study agoraphobia did not reach the HR-QoL impairment level of the major depressive disorder, and its HR-QoL impairment was similar to the one observed for panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, and specific phobia. In recent studies, the impact on HR-QoL of major depressive disorder was found to be similar to the one produced by severe hematological cancers,[33] and post-traumatic stress disorder was found to impair HR-QoL more than panic disorder.[34] Moreover, separate investigations have shown that the impairment of quality of life attributable to the comorbidity with simple phobia depends on conditions in comorbidity and not on the disturbance itself.[35] The findings are consistent with other studies that had seen the co-morbid agoraphobic component affecting the quality of life in a measure not inconsistent with other anxiety disorders.[36,37] Similarly, the impact on quality of life of obsessive-compulsive disorder was found to be influenced by the co-morbidity with bipolar spectrum disorders.[38]

However, the attributable burden of agoraphobia is nonnegligible. When compared to the attributable burden of other chronic and disabling conditions in studies that applied the same methodology of this study, the attributable burden of agoraphobia resulted higher than the attributable found in celiac disease,[39] lower than in multiple sclerosis,[40] or in fibromyalgia,[41] but comparable to the one observed for Wilson disease and eating disorders.[42,43]

Severe role impairment was reported in WHS in arond 1/3 of people diagnosed with agoraphobia. This seems to confirm that the share of people in the general population who receives a diagnosis of agoraphobia often presents severe impairment (WHS) or a strong impairment of quality of life, but this does not apply to all people with agoraphobia equally. The percentage of people with strong impairment of quality of life identi-

fied by our study on the total of people with ICD-10 agoraphobia (40%), seems much closer to the percentage of people with DSM-5 agoraphobia identified by WHS as suffering from a strong impairment (43%), which is a higher percentage of severe impairment among people diagnosed with agoraphobia according to the criteria of the DSM-IV (30%). It should be noted that in this study women reported a higher prevalence of agoraphobia than men. Past studies found that women are more likely than men to stay at home to avoid agoraphobic situations and are also more likely to look for a companion to going outside.[44] This may limit their capacity to optimally functioning and may have contributed to the relatively high percentage of participants with a strong impairment of quality of life in people that were diagnosed with ICD-10 agoraphobia in this study (40%).

Several limitations have to be acknowledged. The study was designed to investigate the prevalence of people diagnosed with the bipolar spectrum, who were estimated to be 4%, but agoraphobia has lower lifetime prevalence. Thus, the frequency of agoraphobia in the study was small, affecting the power to precisely estimate co-morbidity and associations among different disorders. Another limitation is that our study was conducted with a different methodology from most of the comparison epidemiological studies, with the use of clinical interviewers and with the ICD-10 diagnosis, which is not frequent in epidemiological studies.

The study seems to confirm a homogeneous profile in agoraphobia dependent on comorbidity of panic disorder; this profile concerns the associated conditions such as gender, age, anxiety and disorders in comorbidity and the impairment produced in quality of life. The disorder presents itself as a condition capable of producing a serious impairment of the quality of life but not in all the people affected by it.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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