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# EVIDENCE-BASED PSYCHIATRIC CARE

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*Editors-in-Chief*
Emilio Sacchetti, Claudio Mencacci

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# A POOR EVIDENCE-BASED PSYCHIATRY FOR EVE

**Emilio Sacchetti, Claudio Mencacci**

Editors-in-Chief,
Evidence-Based Psychiatric Care;
Past President and President of the Italian Society of Psychiatry

The existence of an association between gender and mental illnesses is clearly reported in the writings of Moudsley, Grisienger, Kraepelin, and Bleuler at the beginning of the era of scientific psychiatry.

Since that time, a large body of research in psychiatry and neurosciences has challenged this issue and many facts have been learned, in addition to the incontrovertible evidence of clear-cut male/female differences in the prevalence of numerous psychiatric disorders.

First of all, it has been clearly learned that sex hormones affect thoughts, emotions, behaviour and cognition.

It has also been learned that genes located in the sex chromosomes plausibly participate in vulnerabilities to specific mental disorders and iatrogenic health effects.

At the same time, it is known that many stressors and trauma are at least partially gender-specific, and that sometimes the expression of epigenetic processes varies according to the sex of the subject.

Furthermore, the brain is charged by multiple sexual dimorphisms relative to cytoarchitecture, grey- and white-matter morphometry, hemispheric asymmetries, gyrification, growth trajectories, biochemistry, metabolism, functional circuits and distribution, structure and modulation of a number of receptor families. Within the same research line, in addiction, mental disorders may play moderating effects on some “physiological” sexual dimorphisms.

In turn, with different degrees of validity and reliability, the gender of the patients with severe mental illness exerts differential effects on numerous clinical variables such as age at disease onset, symptom profile and severity, placebo response, efficacy and safety of psychopharmacological therapies, adherence to prescribed medications, posology, early discontinuations, pharmacokinetics and pharmacodynamics. Last but not least, the influence of gender on effectiveness of medications may be drug-specific to some degree.

Despite these relevant progresses, current knowledge about the impact of gender on psychiatric disorders and their treatment remains strongly subject to two main interdependent criticisms.

The first is that studies focusing on the role of gender in psychiatry continue to be substantially relegated in a niche for experts. Consequently, possibilities of a translational application of information to the daily clinical routine appear hampered.

The second is that a great deal of research in both animals and humans

**Correspondence**

Emilio Sacchetti
emilio.sacchetti@unibs.it

FIGURE 1.
Ludolphus de Saxonia (supposed author). From Le Miroir de Humaine Salvation (The Mirror of Human Salvation), about 1455.

continues to be highly subject to the risk of sex biases. On the one hand, it is for example common to encounter animal studies that involve only males, do not specify the sex of the participants, or exclude the sex variable even from post-hoc sub-analyses [1]. On the other hand, studies centred on psychiatric patients generally include both males and females, but the former are frequently overrepresented. A disproportionate representation of the two sexes is especially maximised in clinical trials where lactating women or those with childbearing potential in absence of adequate contraceptive measures are generally excluded a priori. Furthermore, most of the research in humans has not been powered for independent analyses by gender, and are placated with rough demonstrations of sex-matching between different experimental groups, and do not subdivide women according to pre-, peri- or post-menopausal status.

Taken together, these relevant weaknesses duly explain not only why the product labels of the preponderant majority of psychotropic medications do not mention gender differences of efficacy and tolerability, but also why the most influential health agencies have explicitly recommended a larger enrollment of females in animal and human studies and (have) invited a systematic search for sex-specific differences. Despite the wide number of evidence to the contrary and the influential advice, psychiatric and allied disciplines continue, however, to adopt a largely unisex experimental approach. This favours unjustified generalisations of findings emerging from samples characterised by an unbalanced male/female ratio, and thus denies in daily practice sexual parity at the main expense of women. Furthermore, poor attention to gender-selective effects may preclude or delay the development of new therapies and the recognition of otherwise hidden adverse events.

Without appreciable changes, the label “evidence-based” appears therefore only partially applicable to psychiatry, and women remain at increased risk to pay the highest consequences. Alike almost all other branches of medicine, psychiatry too seems to have forgotten that Eve originates from Adam’s rib (Fig. 1), but it is far from being Adam.

## Reference

[1] Beerya KA, Zuckerb I. *Sex bias in neuroscience and biomedical research*. Neurosci Biobehav Rev 2011;35:565-72.

# RISK ELEMENTS FOR MENTAL HEALTH IN THE MEDICAL PROFESSION: A COMPARISON BETWEEN PSYCHIATRISTS, INTERNISTS, AND SURGEONS

**Gerardo Favaretto[1], Marta Marvilly[2], Antonio Preti[3]**

[1] Mental Health Department, ULSS9 Treviso, Italy;
[2] Department of Public Health, Section of Psychiatry, University of Verona and Integrated Hospital Verona, Italy
[3] Center of Liaison Psychiatry and Psychosomatics, University Hospital, University of Cagliari, Cagliari, Italy and Genneruxi Medical Center, Cagliari, Italy

**Abstract**

**Objectives:** Recent studies have shown that job-related stressful factors can affect the physical and mental health of doctors in different ways, depending on their medical speciality. In our study, we investigated the differences in general and mental health between doctors (136) and the general population (46), comparing three groups of doctors from three different medical fields and one control group of non-medical population.

**Materials and Methods:** We used the Short Form Health Survey (*SF-36*), the COPE, the Professional Quality of Life (Pro-QOL-III), and the Mini International Neuropsychiatric Interview (*M.I.N.I.*).

**Results:** The doctors expressed higher levels of perceived physical health than the control group, but lower perceived mental health in comparison with the control group. Among doctors, Surgeons and Internists had an overall good level of work-related satisfaction and efficient coping strategies. Psychiatrists had five times odds of being classified in a cluster with low levels of job-related satisfaction and a high risk of psychopathology.

**Conclusions:** The presence of this high-risk cluster suggests that young doctors who wish to become Psychiatrists might find it useful to go through an orientation and evaluation stage before choosing their specialty. This at-risk subgroup could also benefit from support and training programs on the topics of work-related stress, psychopathology, and coping mechanisms.

**Key words:** Physicians mental health, Comparison between medical specialties, Psychopathology, Work-related stress, Coping

## Introduction

Many studies report the difficulties that doctors encounter when managing their own health. Doctors tend to underestimate or deny their illnesses – their mental diseases in particular – and are reluctant to see themselves as patients [1 2]. Doctors are often unable to recognize their own psychopathology, or they ascribe it to fatigue or excessive workload [3]. Many studies show clearly that doctors are more prone to work-related and emotional stress than the average general population [4-7]. The prevalence of burnout in doctors seems to be quite high, ranging from 25-60% to 75% in some studies [8 9]. There are evidences that burnout is associated to a reduction in productivity, as seen by the number of sick leave days, the reduction in work ability, and the intent to change job [10]. Doctors affected by work-related stress are at risk of substance abuse, problems in their personal relationships, depression, and even death [11]. When dealing with burnout, doctors often recur to denial and avoidance as the main coping strategies, which do not seem to be very effective [12 13].

**Correspondence**

Gerardo Favaretto
gfavaretto@ulss.tv.it

Some studies indicate that work-related stressful factors can affect the physical and mental health of doctors in different ways, depending on their medical speciality [14] [15]. Psychiatrists, in particular, seem to be exposed to additional stressors because of the complex therapeutic relationship they have with their patients. A study [16] on 3000 Finnish doctors reported that Psychiatrists were the group with less work-related satisfaction, higher preoccupation about their patients and higher psychological distress, in comparison with other medical specialists. However, according to this study, the group of Psychiatrists had also more work resources, more opportunities to control their jobs, and a better team climate; the differences between work satisfaction and stress were not accounted for by personality or private factors. Another paper [17] reported that work conditions affect the wellbeing and the mental health of doctors in different ways depending on their speciality. According to this study, Internists reported a higher effect of work-related stressors (i.e. time pressure, uncertainty, difficult relationship with co-workers) on their mental health (measured by "irritation" and "emotional exhaustion") than other specialists. In another study [18] conducted on more than 2000 Dutch hospital doctors, mental health specialists reported the highest levels of emotional exhaustion, whereas Surgeons had the lowest levels of burnout; Surgeons also appeared to be the group of specialists with the highest level of engagement (a protective factor against burnout).

## Purpose of the study

This paper aims at investigating the health problems of different medical profiles. We evaluated people working in different professional fields and of different ages, comparing doctors from three specialities (Internists, Surgeons, and Psychiatrists) with one control group of non-medical workers. For each group we considered a number of variables, measured by validated instruments, which identify a risk for physical or mental health. The aim of the study was to analyse the risk elements of the medical profession, and identify which medical category is the most exposed to stress and psychopathology and may need support; we focused on Psychiatrists in particular, because they are subject to peculiar stressors in comparison with other specialists [16] [18]. We expected Psychiatrists to have a level of mental health lower than that of Internists and Surgeons.

## Methods

### *Study design and sample*

The study is cross-sectional. The sample is composed of 182 voluntary people, including a group of hospital doctors (136 people, all working in hospitals of the Veneto region, Italy, at the time of sampling), and a control group (46 people) composed of adults working in Veneto (Italy), and employed in the service industry in a non-medical area (i.e. office workers, clerks). The group of doctors was split in three subgroups of similar size and divided according to speciality areas: Internists (n = 39), Surgeons (n = 44), and Psychiatrists (n = 53).

### *Materials*

We asked the volunteers to fill out four anonymous self-administered questionnaires, and each of them was personally asked questions from a structured interview.

The questionnaires were:

a) a form with sociodemographic data and brief anamnestic information (see Appendix), used to assign each participant to the correct group and to detect any confounding factor;
b) Short Form-36 (*SF-36*), a questionnaire on quality of life and general health, validated in its Italian version by Apolone and Mosconi in 1998 [19]; reliability of the SF-36 in the sample, as measured by Cronbach's alpha, was 0.79 (95% CI = 0.75-0.84), which is good for group comparison;
c) Coping Orientation to Problems Experienced (*COPE*), developed by Carver, Scheier and Weintraub (1989) [20] and edited in its Italian version [21]. It is a questionnaire on coping mechanisms that evaluates the strategies and abilities to face stressful events, grouping them in three categories: problem-focused strategies, emotion-focused strategies, maladaptive strategies; reliability of the COPE in the sample, as measured by Cronbach's alpha, was 0.86 (95% CI = 0.83-0.88), which is good for group comparison;
d) Professional Quality Of Life Questionnaire-III (*ProQOLIII*), a questionnaire on professional quality of life specifically intended for the helping professions, which was administered only to the group of doctors; it was translated and adapted in Italian [22]. The questionnaire measures the positive aspect of the helping profession, or Compassion Satisfaction (CS, which is the pleasure deriving from being able to help through one's work); it also measures the negative aspect of helping others

who have experienced suffering, or Compassion Fatigue. Compassion fatigue encompasses both the aspects of Burnout (B, mental and emotional exhaustion that particularly affects people involved in emotionally demanding professions), and Secondary Traumatic Stress (STS, the negative feelings driven by fear and work-related trauma); reliability of the *ProQOLIII*, as measured by Cronbach's alpha, was 0.75 (0.68-0.80), which is acceptable for group comparison;

e) Mini International Neuropsychiatric Interview (*M.I.N.I.*), a structured interview screening major axis-I psychiatric disorders according to DSM-IV and ICD-10. The authors of *M.I.N.I.* are Sheehan and Lecrubier [23], Italian translation by Conti L., Rossi A., Donda P.

## Statistical analysis

Descriptive and multivariable analysis were performed using SPSS software (version 20.0) (SPSS Inc., Chicago, IL, USA). Additional analysis were carried out in R (R Core Team, 2013) using dedicated packages. All tests were two-tailed, with alpha set at $p < 0.05$.

### *Descriptive and explorative analysis*

For discrete (categorical) variables, counts and percentage were reported. For continuous variables, mean with standard deviation and median were reported.
Exploratory analyses were carried out to assess data distribution by a priori defined groups (three groups of physicians and a control group from the community).
Categorical analyses were carried out with Chi-square, with Yates correction whenever necessary. Pearson's or Spearman's rank correlation coefficient was used to test for associations between variables. Continuous variables were analyzed with both parametric (ANOVA) and non-parametric (Kruskal Wallis) univariate analyses. Since groups differed by genre, and continuous measures tested hypothetically related constructs, MANOVA was applied to the scales by taking genre into account. We used both parametric and non-parametric techniques. The non-parametric multivariate analyses were carried out with the method developed by Bathke and colleagues [25] by using "npmv" statistical package in R programming language.

### *Inferential analyses*

After proving that there were differences across groups in the variables of interest, we focused on the hospital doctor samples to test the hypothesis that Psychiatrists had lower levels of mental health than Internists and Surgeons.
The inferential analyses followed a multistep approach. Principal component analysis (PCA) was applied to all subscales defining the physical and mental wellbeing in the hospital doctors group to extract major latent components defining the responses of the participants on the measures of interest. The "FactoMineR" statistical package (Husson et al., 2013) running in R (R Core Team, 2013) was used to carry out the PCA.
These principal components were then entered into a cluster analysis to identify homogeneous subgroups of cases (participants) based on the scoring on these principal components. The PAM (Partitioning Around Medoids) method was used since it is more robust than k-means in the presence of noise and outliers (Medoids are less influenced by outliers), and it works efficiently for small data sets. The "cluster" statistical package (Maechler et al., 2013) running in R (R Core Team, 2013) was used to carry out the PAM.
Finally, a logistic regression was applied to the extracted clusters, using the clusters as a dependent variable and the profession of the hospital doctors as predictors to identify in which clusters the Psychiatrists were more represented, the a priori hypothesis being that they would be in the clusters with the lowest levels of mental health. The logistic regression was carried out in the R statistical environment (R Core Team, 2013).

## Results

### *General characteristics of the sample*

The sample included 89 (48.9%) females and 93 (51.1%) males; males were predominant among Surgeons, whereas females were predominant in the control group (Table I). The mean age of the sample was 47 years (standard deviation [SD]: 8, 7); Internists tended to be 3 years younger than the sample mean. We did not observe any difference among groups about the frequency of life events, whether they be perceived as negative or not (Table I).
There was a trend for age's being negatively related to scores on the questionnaires. In particular, age was negatively related to physical activity (Spearman's rho = -0.342, $p < 0.0001$) and to social activities (rho = -0.204, $p = 0.006$).
Subscales of the SF-36 were closely related to each other at Pearson's $r \geq 0.30$ with very few exceptions ("mental health" and "role limitations due to emotional

**Table I.** General characteristics of the sample.

| | Psychiatrists | Internists | Surgeons | General population | |
|---|---|---|---|---|---|
| **N** | **53** | **39** | **44** | **46** | |
| Sex<br>*Males*<br>*Females* | <br>28 (53%)<br>25 (47%) | <br>18 (46%)<br>21 (54%) | <br>34 (77%)<br>10 (23%) | <br>13 (28%)<br>33 (72%) | $\chi^2 = 22.11$, df = 3, $p < 0.0001$ |
| Age | 48.1 (9.9) | 44.3 (6.7) | 47.4 (8.2) | 47.9 (9.2) | F(3;178) = 1.70, p = 0.167 |
| Marital status<br>*Married/cohabitant* | <br>34 (64%) | <br>29 (74%) | <br>34 (77%) | <br>32 (69%) | $\chi^2 = 2.71$, df = 6, p = 0.844 |
| Educational qualification<br>*University degree/master* | <br>53 (100%) | <br>39 (100%) | <br>44 (100%) | <br>22 (48%) | $\chi^2 = 182.0$, df = 9, $p < 0.0001$ |
| Type of contract<br>*Long term* | <br>53 (100%) | <br>39 (100%) | <br>44 (100%) | <br>42 (91.3%) | $\chi^2 = 12.09$, df = 3, p = 0.007 |
| Duration of employment<br>*More than 10 years* | <br>33 (62%) | <br>26 (67%) | <br>32 (73%) | <br>37 (80%) | $\chi^2 = 4.27$, df = 3, p = 0.223 |
| Life events<br>*Yes, one*<br>*Yes, more than one* | <br>14 (26%)<br>24 (45%) | <br>13 (33%)<br>13 (33%) | <br>9 (20%)<br>17 (38%) | <br>10 (22%)<br>25 (54%) | $\chi^2 = 6.41$, df = 6, p = 0.378 |
| Recent negative events<br>*Yes, one*<br>*Yes, more than one* | <br>12 (22%)<br>3 (6%) | <br>4 (10%)<br>1 (3%) | <br>8 (18%)<br>3 (7%) | <br>5 (11%)<br>3 (6%) | $\chi^2 = 4.86$, df = 6, p = 0.562 |

problems" were poorly related to subscales measuring physical functioning: see Figure A1 in appendix).
In the COPE the two adaptive strategies were related to each other, while the maladaptive strategies were unrelated to them (see Figure A2 in appendix).
In the *PROQoL* of the hospital doctors subsample, the two components of the *Compassion fatigue* were related to each other, and negatively correlated with the *Compassion Satisfaction* subscale (see Figure A3 in appendix).

***Comparison between groups on quality of life scales***

Univariate analysis shows the following differences in the sample concerning quality of life as measured by *SF-36*: less tolerance to physical pain in the general population, more involvement in social activities in the Internists group, more emotional limitations and worse quality of life in relation to mental health among Psychiatrists (see Table II). Psychiatrists also had lower scores on the *Compassion Satisfaction Scale* (CSS) of *PROQoL*, whereas Internists scored marginally lower on the *Secondary Traumatic Stress* (STS) scale of *PROQoL*. On the other hand, Psychiatrists make use of emotion-focused coping strategies more often, and Surgeons resort to maladaptive coping strategies less often than their colleagues. The non-parametric analysis (Kruskal-Wallis test) largely confirmed the results of the ANOVA.

In order to further compare the groups, we adopted a multivariate analysis of variance using the profession group as a predictive factor and the subscales of *SF-36* and *PROQoL* as dependent variables. MANOVA analysis indicated that *SF-36* subscales differentiate the groups of participants: F (3, 178) = 2.02, Wilks's lambda = 0.76, p = 0.003 (Figure B1 in appendix). The differences in the sample were greatly reduced when taking into account the differences of the predictor in relation to genre (F [3, 174] = 1.62, Wilks's lambda = 0.79, p = 0.03).
Regarding the *COPE* subscales, MANOVA analysis showed an important difference in relation to the profession: F (3, 178) = 3.10, Wilks's lambda = 0.85, p = 0.001 (Figure B2 in appendix). Again, this difference was smaller but did not disappear when taking the genre into account (F [3, 174] = 2.17, Wilks's lambda = 0.89, p = 0.02).
For the *PROQoL*, MANOVA indicated an important difference in the subscales in relation to profession among hospital doctors: F (2, 133) = 6.28, Wilks's lambda = 0.76, $p < 0.0001$ (Figure B3 in appendix). However, when considering the genre, the differences between the professional groups lost their statistical significance (F [2, 130] = 1.08, Wilks's lambda = 0.95, p = 0.37)
We repeated the multivariate analysis with the non-parametric method developed by Bathke and colleagues

**Table II.** Distribution of scores in relation to the professional activity.

| | Psychiatrist | Internist | Surgeon | Gen. pop. | ANOVA | Kruskal Wallis |
|---|---|---|---|---|---|---|
| **SF36 (n = 182)** | | | | | | |
| Physical functioning | 93.5 (11.2) | 98.8 (3.7) | 96.1 (10.9) | 94.6 (8.5) | F(3;178) = 2.68, p = 0.048 | $\chi^2$ = 16.1, p = 0.001 |
| Role limitations due to physical health | 87.2 (26.7) | 98.1 (12.0) | 92.0 (23.3) | 94.0 (16.8) | F(3;178) = 2.09, p = 0.102 | $\chi^2$ = 7.5, p = 0.056 |
| Pain | 80.5 (22.9) | 89.2 (15.8) | 86.3 (18.7) | 75.2 (21.6) | F(3;178) = 4.09, p = 0.008 | $\chi^2$ = 10.9, p = 0.012 |
| General health | 70.8 (14.9) | 72.7 (11.6) | 72.3 (10.8) | 68.9 (12.4) | F(3;178) = 0.78, p = 0.507 | $\chi^2$ = 2.4, p = 0.479 |
| Energy | 55.0 (14.5) | 62.8 (17.3) | 58.5 (12.7) | 55.7 (16.5) | F(3;178) = 2.30, p = 0.079 | $\chi^2$ = 7.8, p = 0.049 |
| Social functioning | 71.2 (21.9) | 87.1 (17.6) | 77.1 (19.5) | 75.6 (17.2) | F(3;178) = 5.16, p = 0.002 | $\chi^2$ = 14.9, p = 0.002 |
| Role limitations due to emotional problems | 71.5 (33.7) | 87.8 (21.1) | 86.9 (22.0) | 87.5 (19.3) | F(3;178) = 4.98, p = 0.002 | $\chi^2$ = 9.2, p = 0.027 |
| Mental health | 67.2 (14.2) | 77.1 (14.2) | 70.3 (13.1) | 71.6 (12.7) | F(3;178) = 4.04, p = 0.008 | $\chi^2$ = 11.4, p = 0.010 |
| **PROQoL (n = 136)** | | | | | | |
| CSS | 32.0 (6.6) | 36.1 (5.8) | 37.5 (5.3) | -- | F(2;133) = 10.9, p < 0.0001 | $\chi^2$ = 19.2, p < 0.0001 |
| BS | 18.9 (5.6) | 17.4 (4.9) | 17.8 (5.8) | -- | F(2;133) = 0.96, p = 0.385 | $\chi^2$ = 1.4, p = 0.483 |
| STSS | 10.6 (6.1) | 8.9 (4.5) | 12.3 (7.6) | -- | F(2;133) = 3.19, p = 0.044 | $\chi^2$ = 3.8, p = 0.146 |
| **COPE** | | | | | | |
| Problem-focused strategies | 77.1 (10.7) | 73.8 (10.5) | 74.9 (11.9) | 74.9 (7.1) | F(3;178) = 0.88, p = 0.449 | $\chi^2$ = 5.9, p = 0.001 |
| Emotion-focused strategies | 72.1 (12.7) | 66.7 (13.1) | 62.8 (10.3) | 64.0 (11.7) | F(3;178) = 5.77, p = 0.001 | $\chi^2$ = 16.4, p = 0.001 |
| Maladaptive strategies | 32.8 (5.3) | 31.0 (5.6) | 29.6 (4.4) | 32.4 (4.5) | F(3;178) = 4.02, p = 0.008 | $\chi^2$ = 13.3, p = 0.004 |

(Bathke et al., 2008; Liu et al, 2011). The non-parametric analysis confirmed that the differences among the groups were statistically significant on the *SF-36* (F-approximation = 3.693, p < 0.0001; with genre, F-approximation = 5.465, p < 0.0001), and the *COPE* (F-approximation = 3.858, p < 0.0001; with genre, F-approximation = 6.739, p < 0.0001). On the *PROQoL*, again, when taking the genre into account, the differences between the professional groups were no longer statistically significant (F-approximation = 4.055, p = 0.004; with genre, F-approximation = 2.566, p < 0.059).

***Psychiatric diagnoses with M.I.N.I.***

The results of *M.I.N.I.* confirmed the low prevalence of mental health diseases in the Italian population, with estimated rates between 2% and 10% depending on the diagnosis. The main differences between the general population and the doctors were the absence of Panic Disorder among Surgeons (0%), whereas its prevalence was 15% in the general population, 17% among Psychiatrists, and 8% among Internists. We also observed that Psychiatrist admitted to use anxiolytic and hypnotic drugs more (15.1%) than Internists (5.1%), Surgeons (who denied using them, 0%), and the general population (0%). These prevalence rates should be taken as approximate, because each sample consisted of less than 100 units.

***Principal component analysis of the SF-36, COPE and PROQoL in the hospital doctors subsample***

In order to better understand the relationship between the professional groups and the variables measuring

quality of life and general health, coping strategies and professional satisfaction, we applied PCA to the subscales of the *SF-36*, the *COPE* and the *PROQoL*. The algorithm extracted three principal components with eigenvalues above 1. Overall cumulative explained variance was 58%.

The first dimension summarizes the degree of life satisfaction, with greater loading of the SF-36 subscales measuring items related to mental health. The second dimension summarizes dissatisfaction with the helping profession, with positive loading of the two subscales of the Compassion fatigue section of the *PROQoL* and negative loading of the *Compassion Satisfaction* subscale. The third dimension measures the involvement of participants in coping strategies.

The first two dimensions group participants into four quadrants (Figure 1).

Increasing scores on the first dimension, left to right, are related to better quality of life. Increasing scores on the second dimension (along the vertical axis, bottom to top) are related to greater dissatisfaction with the helping profession, hence higher scores on the Burnout and the Secondary traumatic stress subscales.

Higher scores on the Compassion satisfaction subscale occur in the lower right quadrant, corresponding to higher scores on the first dimension and lower scores on the second dimension. On the other hand, higher scores on the subscale of problem-focused strategies of the COPE occur in the lower left quadrant, corresponding to lower scores on both the first and the second dimensions. Apparently, problem-focused strategies are active in the presence of poor quality of life, but they do buffer the impact of stress, limiting dissatisfaction with the helping profession. The other two strategies, those focused on emotions and maladaptive strategies, seem less effective in buffering the impact of stress on professional satisfaction.

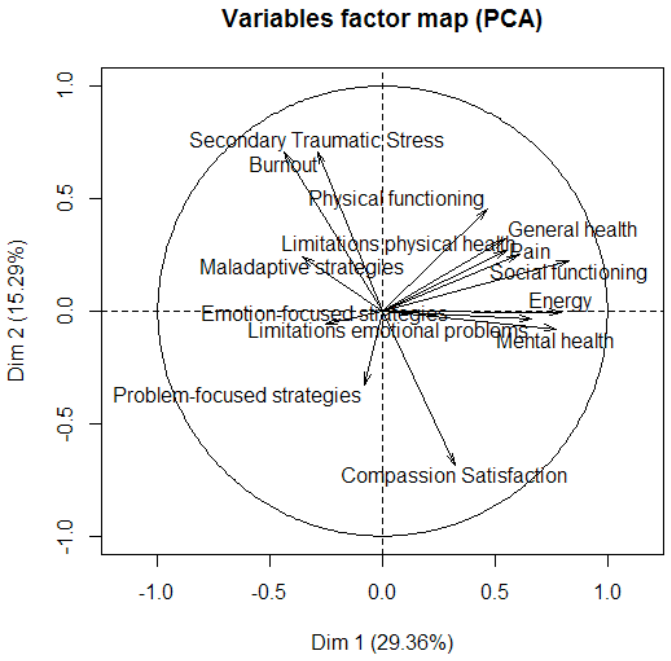


FIGURE 1.
Variables factor map (PCA).

Psychiatrists scored higher than Internists on the first PCA dimension, the two groups of hospital doctors did not differ on the second PCA dimension, Psychiatrists scored higher than Surgeons on the third PCA dimension (Kruskal-Wallis test with Dunn post-hoc test; Figure 2).

Across the three PCA dimensions Psychiatrists tended to be placed towards the less positive side of the components extracted by the PCA, while Internists tended to be placed towards the more positive side of the same components, with Surgeons somehow in between (Figure C1 in appendix).

### *Partitioning Around Medoids cluster analysis of the three dimensions extracted by principal component analysis in the hospital doctors subsample*

The three dimensions extracted by the PCA were entered into a PAM cluster analysis.

The best solution had two, partially overlapping clusters explaining 68% of total variance in the variables (the three PCA dimensions). The first cluster included 75 participants (55%), while the second cluster included 61 participants (45%) and was better defined than the first cluster (Figure 3, right side concerning the silhouettes).

Cluster 1 scored lower than cluster 2 on the first PCA dimension that measures quality of life, and scored higher than cluster 2 on the second PCA dimension, the one measuring dissatisfaction with the helping profession. No differences were found on the third PCA dimension, i.e. coping strategies (Mann–Whitney U test, Figure 4).

### *Logistic regression of hospital doctors by profession on the clusters extracted by the PAM analysis*

We tested the hypothesis that Psychiatrists would more likely fall in cluster 1, the one with poorer quality of life and greater dissatisfaction with the helping profession, than in cluster 2. Genre and age were taken into account because of their inequality across professions.

Compared to Internists, Surgeons had four times odds of being classified in cluster 1, and Psychiatrists had five times odds of being classified in cluster 1 (Table IV).

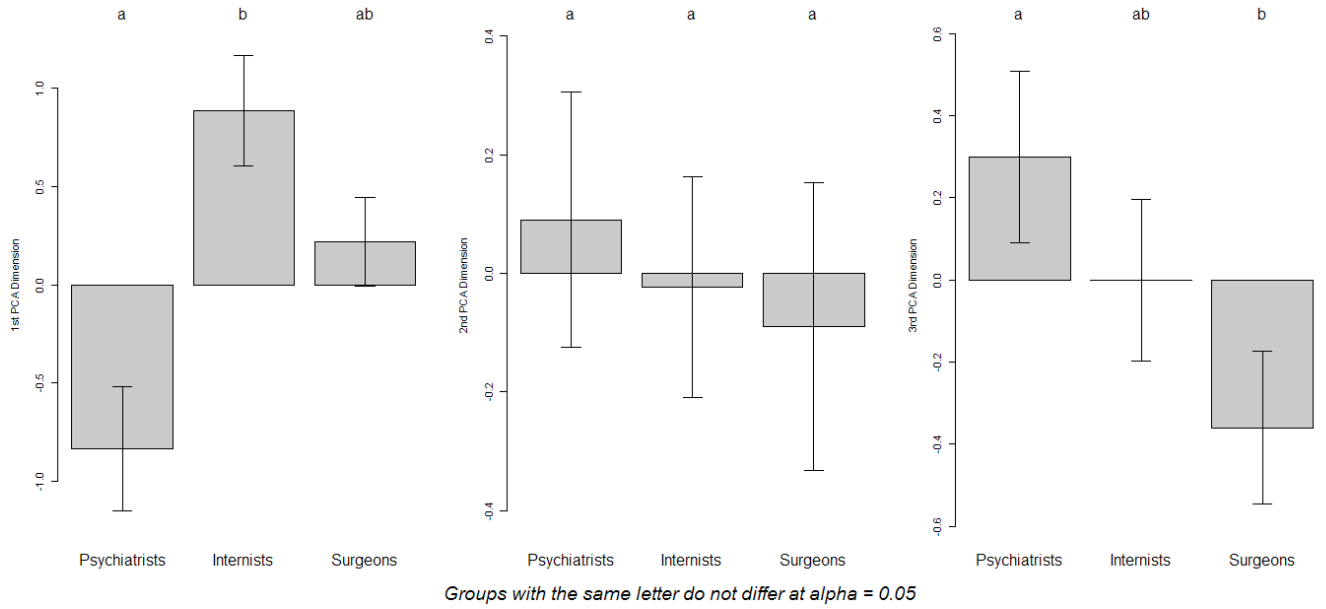


FIGURE 2.

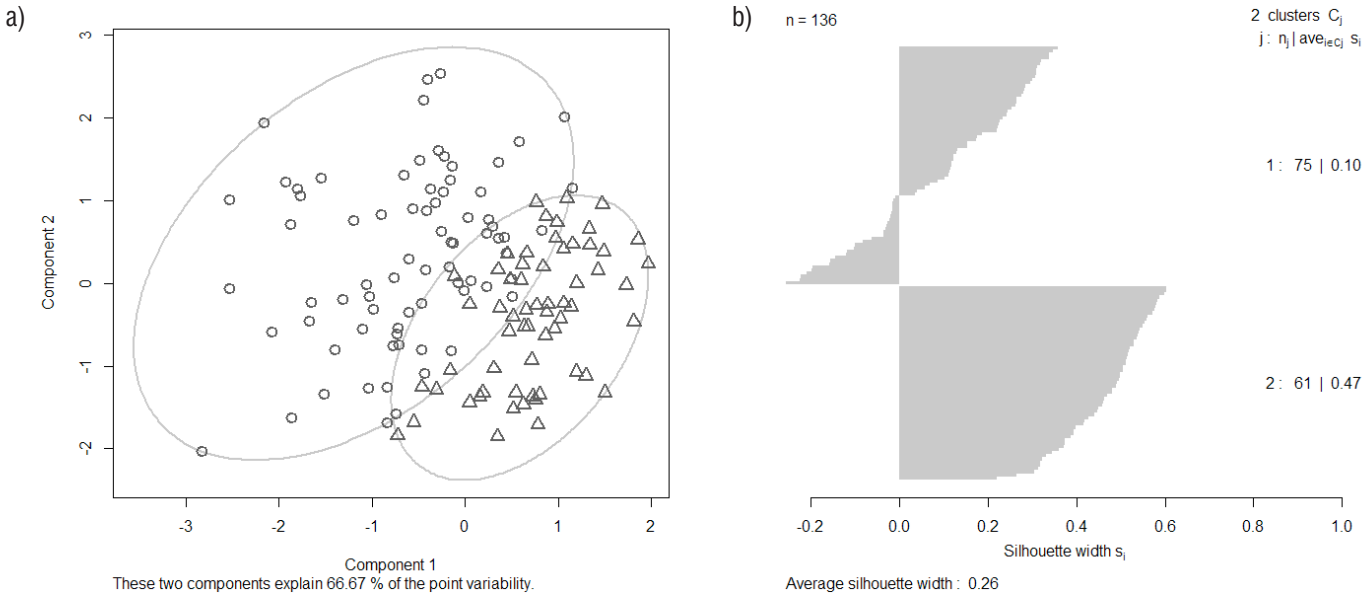


FIGURE 3.

a) Bivariate plot (Clusplot) of the data after PAM clustering. b) Silhoutte plot of PAM cluster of PCA dimesions.

The model had a reasonable fit (Likelihood ration test = 20.38, df = 4, p = 0.0021) and accuracy, as measured by the area under the ROC curve (AUC), was acceptable (70.1%; 95% CI: 61.4%, 78.8%), albeit modest. Explained variance was between 11% and 18% depending on the method used to calculate it.

## Discussion

The results of this study are consistent with other works in the literature concerning the differences between specialists in terms of professional quality of life. In agreement with the literature [4-7] we found that doctors generally have a better physical health than the general population (which on the contrary has a higher level of physical pain and a lower level of physical functioning). As far as mental health is concerned, the control group seemed to have a better perceived mental health and less role limitations due to emotional problems than Surgeons, and Psychiatrists in particular.

Concerning the professional quality of life of the help-

**Table III.** Principal component analysis of the variables extracted as discriminant.

| | Dimension 1 | Dimension 2 | Dimension 3 |
|---|---|---|---|
| Physical functioning – SF36 | -0.17 | -0.07 | 0.86 |
| Mental health – SF36 | -0.48 | 0.34 | 0.47 |
| CSS – PROQoL | -0.29 | 0.70 | 0.01 |
| STSS – PROQoL | 0.34 | -0.66 | 0.31 |
| Problem-focused strategies – COPE | 0.48 | 0.67 | 0.05 |
| Emotion-focused strategies – COPE | 0.80 | 0.40 | 0.17 |
| Maladaptive strategies – COPE | 0.74 | -0.08 | 0.14 |
| | | | |
| Eigenvalues | 1.90 | 1.69 | 1.13 |
| % variance explained | 27.2% | 24.2% | 16.2% |
| % cumulative variance | 27.2% | 51.3% | 67.5% |
| The values in column represent the loading of each variable on the factors (called "dimensions"). Factorial loading higher than 0.50 are in bold, and they indicate a bigger loading of the corresponding variables. | | | |

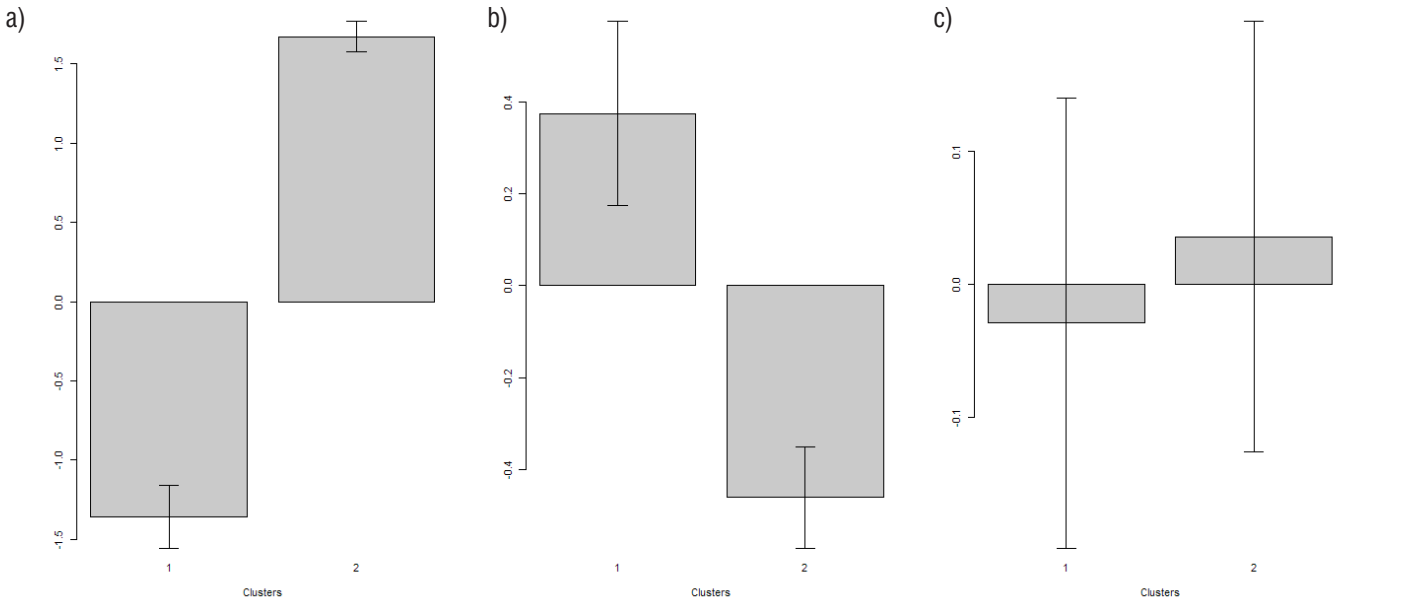


FIGURE 4.
a) PCA Dimension 1 (Explained variance: 29.3%). b) PCA Dimension 2 (Explained variance: 15.3%). c) PCA Dimension 3 (Explained variance: 13.3%).

ing professions as measured by ProQOL scale, we found that Psychiatrists reported the lowest professional satisfaction compared to Surgeons and Internists. Surgeons reported the highest level of professional satisfaction but also the highest level of traumatic stress, whereas Internists were less at risk, with a good professional satisfaction and a low level of traumatic stress.

Coping strategies were different depending on the medical specialty. Psychiatrists were the group who used coping strategies the most, especially those based on emotions, but also maladaptive ones (i.e. denial, mental disengagement, behavioural disengagement). The group of Surgeons showed a good level of problem-focused strategies, a low use of emotion-focused strategies, and used maladaptive strategies less than their colleagues.

As far as M.I.N.I. is concerned, we found that the main difference among groups was the prevalence of panic disorder, which was totally denied by Surgeons (0%), admitted by 15% of the general population, 17% of Psychiatrists, and 8% of Internists. We also noted that the use of anxiolytic and hypnotic drugs was higher among Psychiatrists (15.1%),

**Table IV.** Distribution of the variables object of study in three clusters extracted by PAM.

| | Cluster 1 | Cluster 2 | Cluster 3 | |
|---|---|---|---|---|
| Profession<br>*Psichiatrist*<br>*Internist*<br>*Surgeon* | <br>30 (47%)<br>16 (25%)<br>18 (28%) | <br>17 (50.0%)<br>8 (23%)<br>9 (27%) | <br>6 (16%)<br>15 (39%)<br>17 (45%) | $\chi^2$ = 12.0, p = 0.017 |
| Sex<br>*Males*<br>*Females* | <br>35 (55%)<br>29 (45%) | <br>15 (44%)<br>19 (56%) | <br>30 (79%)<br>8 (21%) | $\chi^2$ = 9.84, p = 0.007 |
| Age | 47.1 (8.6) | 46.1 (8.3) | 46.9 (9.1) | F(2;133) = 0.15, p = 0.859 |
| Negative events<br>*One*<br>*More than one* | <br>14 (22%)<br>4 (6%) | <br>7 (20%)<br>2 (6%) | <br>3 (8%)<br>1 (2%) | $\chi^2$ = 4.55, p = 0.336 |
| **SF36** | | | | |
| Physical functioning | 93.9 (12.1) | 96.9 (9.0) | 98.3 (3.1) | F(2;133) = 2.72, p = 0.069 |
| Physical limitations | 87.5 (27.1) | 93.4 (22.4) | 98.0 (8.8) | F(2;133) = 2.76, p = 0.067 |
| Pain | 83.3 (22.8) | 81.8 (19.8) | 90.3 (13.1) | F(2;133) = 2.02, p = 0.136 |
| General health | 69.8 (13.7) | 73.1 (12.6) | 73.9 (10.7) | F(2;133) = 1.48, p = 0.230 |
| Energy | 57.0 (15.0) | 53.5 (15.1) | 65.0 (13.0) | F(2;133) = 6.11, p = 0.003 |
| Social functioning | 74.3 (21.5) | 72.6 (21.9) | 87.9 (14.8) | F(2;133) = 7.04, p = 0.001 |
| *Emotional limitations*<br>78.4 (28.2)<br>72.3 (33.4)<br>93.7 (15.4) | | | | F(2;133) = 6.36, p = 0.002 |
| Mental health | 70.5 (13.7) | 63.9 (15.3) | 78.4 (10.9) | F(2;133) = 10.6, p < 0.0001 |
| **PROQoL** | | | | |
| CSS | 37.0 (5.0) | 28.5 (5.4) | 37.3 (5.4) | F(2;133) = 34.7, p < 0.0001 |
| BS | 16.6 (4.5) | 23.7 (4.3) | 15.7 (4.6) | F(2;133) = 35.5, p < 0.0001 |
| STSS | 8.6 (3.9) | 17.2 (7.4) | 8.3 (4.2) | F(2;133) = 37.3, p < 0.0001 |
| **COPE** | | | | |
| Problem-focused | 82.6 (8.6) | 69.6 (9.4) | 68.8 (8.9) | F(2;133) = 38.3, p < 0.0001 |
| Emotion-focused | 76.1 (8.8) | 66.7 (10.4) | 54.7 (7.7) | F(2;133) = 68.7, p < 0.0001 |
| Maladaptive | 32.9 (4.2) | 33.4 (5.7) | 26.4 (2.6) | F(2;133) = 32.8, p < 0.0001 |

much lower among Internists (5%) and totally denied by Surgeons and the control group (0%). This result is probably underrated. However, although Psychiatrists admitted to use this category of drugs, none of them was diagnosed with abuse or addiction. Most likely, Psychiatrists make use of anxiolytic and hypnotic drugs more than their colleagues probably because they have a better knowledge of the pharmacodynamics of these substances, are more familiar with them, and have easier access to them than other specialists.

Psychiatrists generally reported a low quality of life in terms of mental health. This fact can be explained by a specific professional inclination, which makes Psychiatrists more sensitive to mental health in general and makes them more open about admitting problems in this area. However, this hypothesis explains the differences of the professional quality of life only partially. It is reasonable to think that there could be a risk element, strictly related to the kind of profession, that has an influence on the psychiatrists group only and not on the others. We also observed that, on the contrary, Surgeons and Internists had generally a more concrete and proactive attitude (as seen from the distribution of coping strategies), with a lower level of mentalization. This could explain the tendency, among Surgeons, to feel high professional satisfaction together with high traumatic stress, as if there was a sudden transition from a good work functioning to a problematic and highly stressful situation. PCA obtained three principal dimensions that explain most of the sample variance. PCA results showed

that Psychiatrists were the ones who differed significantly from the other professions, with fewer differences between Internists and Surgeons.
Cluster analysis with PAM method allowed us to identify two clusters of subjects. The more problematic cluster - in terms of low professional quality of life and greater dissatisfaction with the helping profession - was made up of Psychiatrists mainly, whereas the cluster with the lowest risk of psychopathology and the best psychological functioning was made up of Internists mainly.
The greater presence of Psychiatrists in the worst cluster psychologically probably reflects the complexity of feelings about personal satisfaction and the difficulty in expressing their own emotional well-being. Improved coping abilities might benefit the subgroups of doctors with the worst professional functioning, because they would improve their quality of life and reduce the risk of chronic psychopathology in the long run.
The presence of a group of Psychiatrists at risk of psychopathology, as emerged from this study, suggests that the need to test and evaluate the professional quality of life is probably underestimated. A good number of doctors might benefit from specific support and motivation programs, especially among the mental health profession. In view of a continuation of this study, it might be useful to verify the effectiveness of these support programs with a case-control study.
Some of the doctors reported to barely use efficient coping strategies: this might imply that they have a certain difficulty in dealing with problems and stressful situations on the workplace, which may lead to a reduced work functioning and even possible damage to the patient. For this reason, it might be useful to elaborate training programs based on these aspects, which should be considered as well when selecting young doctors to become Psychiatrists.
One major limitation of the study is the small sample size. This precluded the evaluation of potential moderators or mediators in the differences by group. Small sample size studies are also more prone to false-positive results, or may over-estimate the magnitude of the observed effect size [26]. However, small sample size studies have also some strength. A small number of participants can be enrolled in a short space of time, and with a small number of participants a few centers can be involved, thus limiting the variance between units [26]. An additional strength of the study is the use of state-of-the-art statistics, in both the exploratory and inferential part of the investigation. We feel the results of the study open the space to a large, inter-collaborative study aimed at replicating and extending the findings described in this article.

## Conclusions

The comparison of different specialties allowed us to identify a group of doctors with a good professional satisfaction and efficient coping strategies, made up of Surgeons and Internists especially. Psychiatrists appear to be divided into two subgroups, one with good work functioning and the other with the lowest levels of satisfaction, the highest traumatic stress, and maladaptive coping strategies. The second subgroup could be at risk of developing psychopathology, which may be related to a specific professional inclination or may be the result of work exposure itself. The subgroup of doctors at risk might benefit from professional motivation and coping support programs. Moreover, these results suggest the expediency of improving the existing training and selection programs of young doctors who wish to become Psychiatrists.

## Take home messages for psychiatric care

- Doctors have better perceived physical health but worse perceived mental health, compared to the general population
- Among doctors, Psychiatrists have five times odds of being classified in a cluster with low levels of job-related satisfaction and a high risk of psychopathology
- Some of the doctors reported to barely use efficient coping strategies when dealing with problems and stressful situations at the workplace. This may lead to reduced work functioning and even possible damage to the patient
- A good number of doctors might benefit from specific support and motivation programs, especially among the mental health profession, to reduce the risk of burnout

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## Appendix

Sociodemographic questionnaire.

| |
|---|
| Age |
| Sex |
| Marital status (specify if divorced or separated) |
| Number of children |
| Educational qualification |
| Employment |
| Duration of employment |
| Type of employment contract (long term/part time) |

How many times in your life did you change your job or work place?

NEVER ❍
ONCE ❍
MORE THAN ONCE ❍

Did you experience any particularly negative life events in the last 12 months?
For example: divorce, diseases, serious work problems, …

NEVER ❍
ONCE ❍
MORE THAN ONCE ❍

Have you ever been exposed to life events that you would describe as extremely traumatic?
For example: assault, bereavements, …

NEVER ❍
ONCE ❍
MORE THAN ONCE ❍

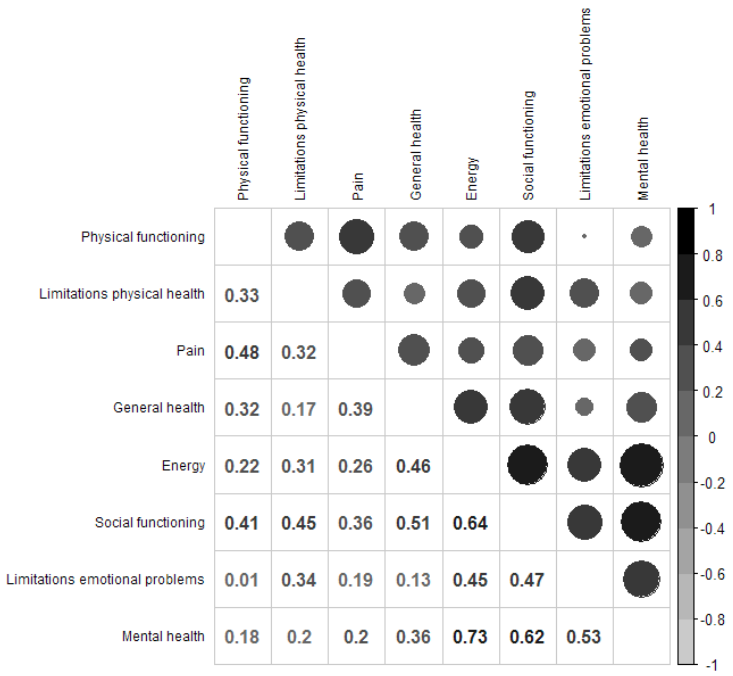


FIGURE A1.
All correlations with r > ±0.15 had p < 0.05.

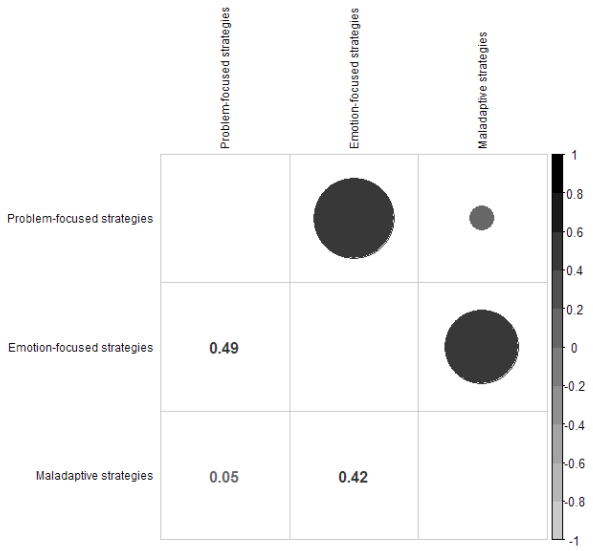


FIGURE A2.
All correlations with r > ±0.15 had p < 0.05.

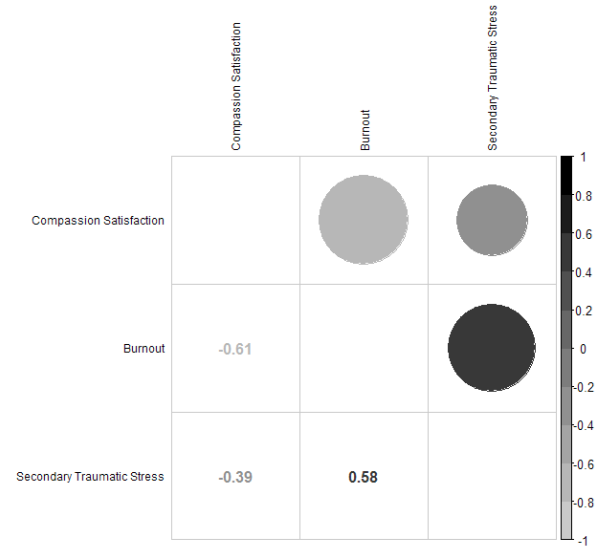


FIGURE A3.
All correlations with r > ±0.15 had p < 0.05.

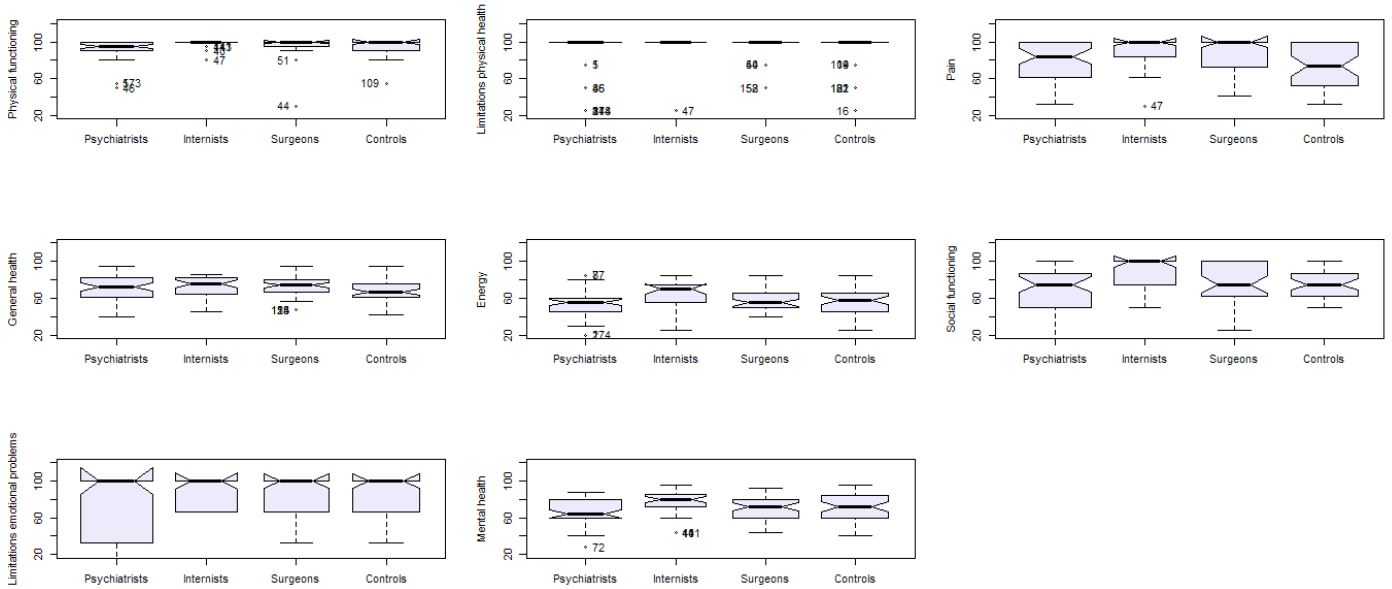


FIGURE B1.
SF36 - Distribution of scores by professional group.

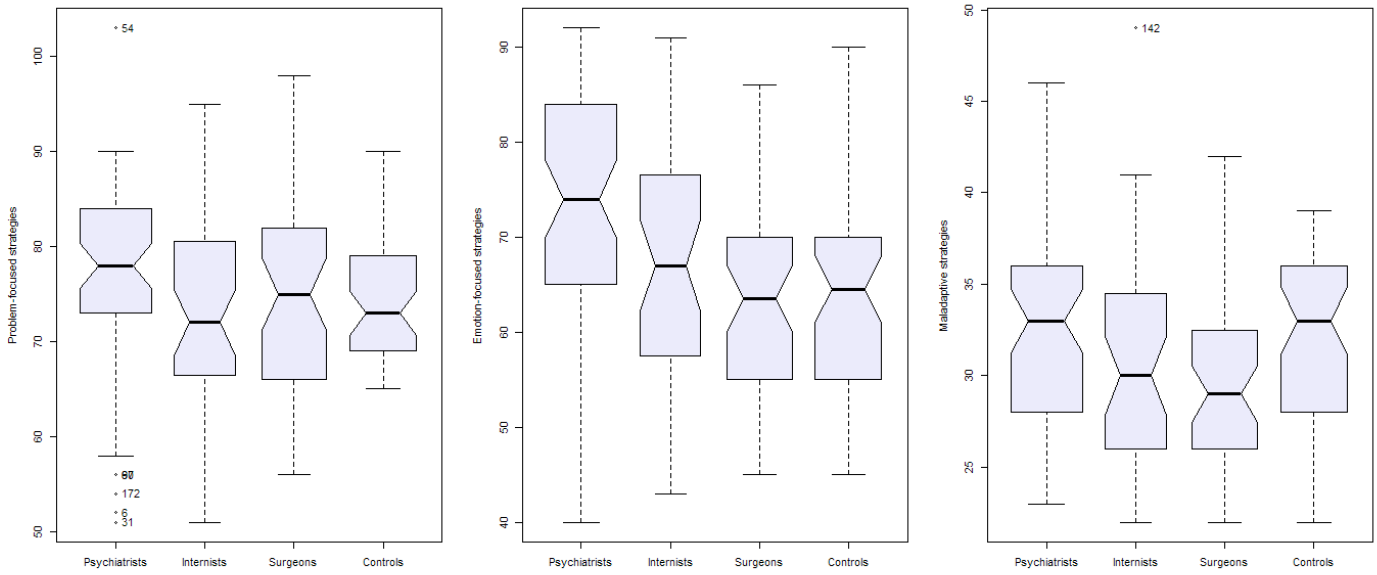


FIGURE B2.
COPE - Distribution of scores by professional group.

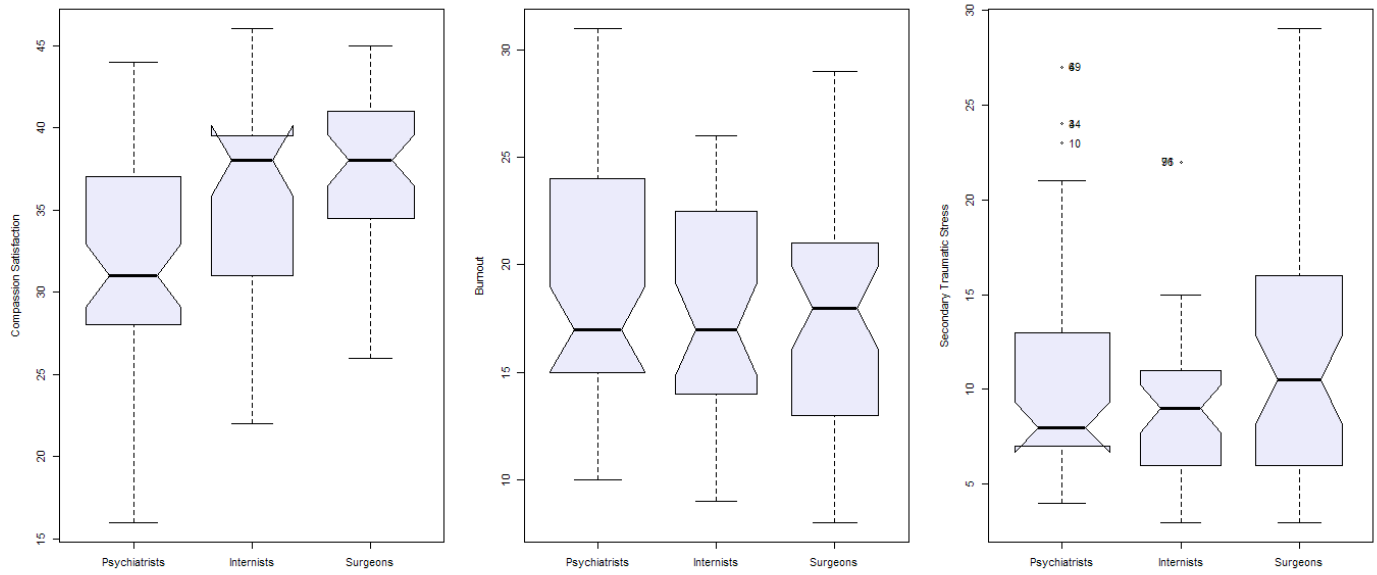


FIGURE B3.
PROQoL - Distribution of scores by professional group.

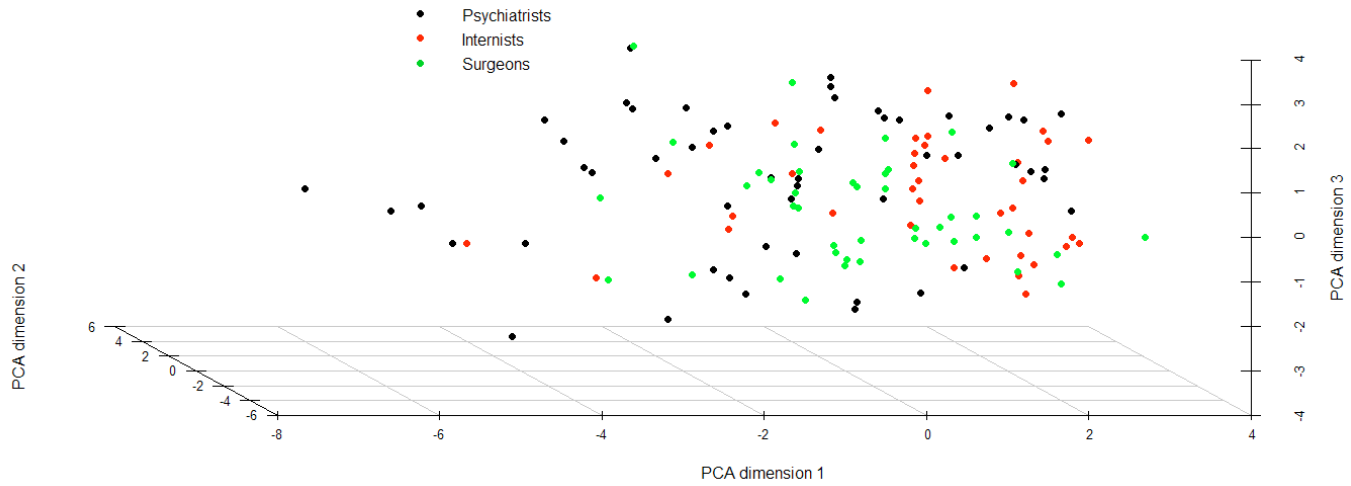


FIGURE C1.

Tridimensional distribution of scores along the three man PCA in the sample.

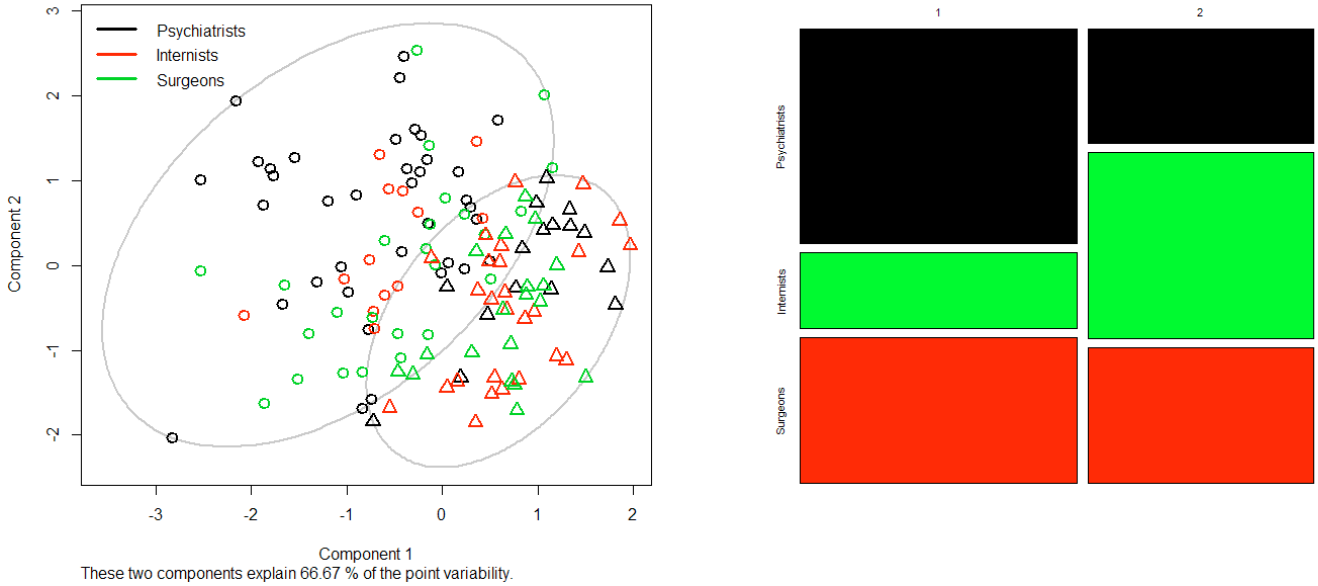


FIGURE D1.

a) Bivariate plot (Clusplot) of the data after PAM clustering. b). Distribution of hospital doctors in the three clusters.

**Giancarlo Cerveri[1], Camilla Gesi[1,2], Anna Omboni[1], Giovanni Migliarese[1], Simone Vender, Claudio Mencacci[1]**

[1] Department of Neuroscience, Clinical Psychiatry, Ospedale Fatebenefratelli and Oftalmico, Milan, Italy; [2] Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa, Pisa, Italy; [3] Department of Clinical and Experimental Medicine, Insubria University of Varese, Varese, Italy

# METABOLIC SYNDROME AND CARDIOMETABOLIC RISK AMONG PATIENTS WITH SEVERE MENTAL ILLNESS FROM AN ITALIAN COMMUNITY MENTAL HEALTH SERVICE

**Abstract**

**Objectives:** The study aimed to investigate the cardiometabolic health in a sample of patients with severe mental illness from an Italian Community Mental Service.

**Material:** Of 77 patients enrolled, 46.5% smoked cigarettes, 58.1% of patients were overweight, 17% had hypertension. Diabetes, high levels of fasting triglyceride and low levels of fasting HDL-C were present in 5.1%, 47.5% and 40.0% of subjects respectively. 31.4% of patients had Metabolic Syndrome.

**Results:** A significant correlation between the length of antipsychotic exposure and BMI, waist circumference, LDL-C and fasting glucose was found only in the subsample of subjects with less than 15 years of illness.

**Conclusions:** Our results highlight the need to implement appropriate cardiovascular risk assessment and prevention in Mental Health Services.

**Key words:** Metabolic Syndrome, Severe Mental Illness, Community Mental Health, Cardiovascular Risk

## Introduction

People with Severe Mental Illness (SMI) show a greater cardiometabolic risk than the general population, resulting in in a 2-3 fold increased mortality, primarily from cardiovascular disease (CVD), and up to 20% reduction in life expectancy in this population [1]. Poor diet, sedentary lifestyle, smoking and the antipsychotic agents prescribed to treat mental health conditions are among the causes of this elevated risk for CVD.

Many of CVD-related risk factors are modifiable by changing unhealthy lifestyles and, when indicated, by referring for treatment. Nevertheless, people with SMI may often choose to avoid health services and the Community Mental Health team may represent the only health professionals who have contacts with them [2]. Despite the development of guidelines recommending an active role of psychiatrists in the management of CVD-related risk factors, Mental Health Services do not appear to be implementing appropriate screening of cardiovascular risk factors within current systems. So that, the physical health management of the severe mentally ill population remains inadequate [3]. On the other hand, little is known about the trajectory of cardiometabolic risk as patients progress through their illness and the few data available are mostly limited to samples assessed in controlled trials or in academic settings.

The present study aims to investigate the cardiometabolic health of

**Correspondence**

Giancarlo Cerveri
giancarlo.cerveri@gmail.com

patients with SMI enrolled in a Community Mental Service in northern Italy. Specifically, the presence of Metabolic Syndrome (MetS) and individual cardiometabolic risk factors will be evaluated in relation to sex, illness duration, and antipsychotic treatment duration.

## Methods

Subjects were recruited in two outpatient centers of the Community Mental Health Service of the Azienda Ospedaliera Fatebenefratelli e Oftalmico in Milan (Italy) between may 2007 and april 2008.
Inclusion criteria were: a) being aged 18 to 75 years; b) being diagnosed as having schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, or bipolar disorder. The following were exclusion criteria: a) being diagnosed as having substance-induced psychotic disorder, or psychotic disorder due to a general medical condition; b) having current neurological disorders affecting diagnosis or prognosis. Any treatment received prior to and after study assessment was based on the community clinician's choice. After receiving a complete description of the study and providing written informed consent, eligible subjects were administered the Structured Clinical Interview for DSM- IV Axis I Disorders (SCID-I) to ascertain the inclusion diagnoses. Informations about demographic variables, prescribed medication, illness duration, were also collected. Moreover, patients underwent assessments of height, weight, waist circumference, and systolic and diastolic blood pressure as well as fasting phlebotomy for levels of glucose, hemoglobin A1c ($HbA_{1c}$), and lipids.
In proceeding with guidelines of the National Cholesterol Education Program-Third Adult Treatment Panel [4], MetS was defined as the presence of at least three of the five criteria including: 1) abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women); 2) hypertriglyceridemia (≥ 1.7 mmol/l or 150 mg/dl); 3) low high-density lipoprotein cholesterol (HDL-C) (Men: < 1.03 mmol/l or 40 mg/dl; Women: < 1.29 mmol/l or 50 mg/dl); 4) raised blood pressure (≥ 130/≥ 85 mmHg); 5) impaired fasting glucose (≥ 5.6 mmol/l or 100 mg/dl).

## Statistics

Beyond descriptive analysis of the entire sample, categorical and continuous cardiovascular variables were compared by sex using $\chi^2$ test and t test respectively. Several Pearson's tests were carried out to evaluate correlations between illness and treatment duration and cardiometabolic parameters, both in the overall sample and in the two sub-sample of subjects with more/less of 15 years of illness. Analyses were performed using SPSS Statistical Package version 20.0 [5].

## Results

The study sample included 77 patients. The mean (SD) age of patients was 45.3 (12.2) years; 46.5% of patients were male. Diagnoses included schizophrenia (37.6%), schizoaffective disorder (18.2%), bipolar disorder (15.3%), and psychotic disorder not otherwise specified or delusional disorder (28.2%). 96.5% were currently receiving antipsychotics, of which 90.7% were second-generation antipsychotics. The mean (SD) illness duration was 15.5 years (12.5), while the mean (SD) total life-time antipsychotic treatment was 7.8 years (9.3).
33.7 of subjects were taking only antipsychotic treatment. Other psychotropic medications consisted mainly of antidepressants (18.6%), benzodiazepines (16.3%) and mood stabilizers (14.0%).
Demographic and clinical characteristics of study sample dichotomized by sex are described in Table I. No differences were found for age, occupational status, education nor for inclusion diagnosis or pharmacological treatment.

## Coronary Heart Disease (CHD) risk factors

Among all patients, 46.5% smoked cigarettes, with no significant differences between males and females. The mean (SD) BMI was 27.3 (6.1). Overall, 58.1% of patients were overweight. Females did not differ from males with regard to weight status, waist circumference or BMI (Table I). Among the patients, 17% had hypertension. Females did not differ from males with regard to systolic and diastolic blood pressure. Impaired fasting glucose levels were present in 11.7% of patients and diabetes in 5.2%. No differences in fasting glucose and HbA1c were found between males and females. Fasting triglyceride levels over 150 mg/dl were present in 45.7% of subjects. Overall, 40.0% of subjects had low levels of fasting HDL-C (less than 40 mg/dl for males and 50 mg/dl for females). As expected, males had lower HDL-C ($p < .001$) than females. 31.4% of patients had MetS. Males and females did not show differences in the

**Table I.** Socio-demographic and clinical characteristics of sample by gender..

| | Male (n = 37) | Female (n = 40) | Chi2/T | p |
|---|---|---|---|---|
| Age | 43.9 (11.9) | 45.5 (14.2) | -.570 | .570 |
| Education (years) | 12.7 (3.5) | 13 (3.8) | .354 | .724 |
| Occupied | 12 (33.3) | 21 (53.8) | 3.197 | .103 |
| **Diagnosis (77 valid)** | | | | |
| Schizophrenia | 16 (43.2) | 15 (37.5) | .264 | .389 |
| Bipolar Disorder | 6 (16.2) | 5 (12.5) | .217 | .750 |
| Delusional/Psychotic NOS | 10 (27.0) | 11 (27.5) | .002 | 1 |
| Schizoaffective Disorder | 5 (13.5) | 9 (22.5) | 1.043 | .382 |
| **Treatment** | | | | |
| BDZ | 6 (16.2) | 6 (14.6) | .037 | 1 |
| Antidepressants | 4 (10.8) | 11 826.8) | 3.213 | .090 |
| Mood Stabilizers | 4 (10.8) | 6 (14.6) | .254 | .740 |
| BMI | 28.2 (5.7) | 26.6 (6.4) | -1.195 | .236 |
| Smoking | 23 (57.5) | 17 (39.5) | 2.679 | .126 |
| Overweight | 24 (70.6) | 23 (60.5) | .802 | .460 |
| Waist circumference | 99.2 (14.5) | 94.1 (13.4) | -1.511 | .135 |
| Exercise | 19 (51.4) | 17 (45.9) | .216 | .816 |
| Blood pressure<br>• Systolic<br>• Diastolic | <br>128.3 (18.6)<br>80.0 (9.5) | <br>120.5 (11.4)<br>79.5 (9.2) | <br>1.661<br>.185 | <br>.106<br>.854 |
| Lipid metabolism<br>• Total cholesterol<br>• HDL-C<br>• LDL-C<br>• Triglycerides | <br>208.4 (46.8)<br>45.7 (14.2)<br>120.2 (34.4)<br>198.4 (138.6) | <br>214.8 (49.5)<br>58.8 (15.6)<br>123.8 (37.3)<br>150.0 (140.2) | <br>.590<br>3.803<br>.414<br>-1.530 | <br>.557<br>**.000**<br>.678<br>.130 |
| Carbohidrate metabolism<br>• Fasting glucose<br>• $HbA_{1c}$ | <br>102.2 (37.3)<br>5.87 (2.1) | <br>93.6 (14.0)<br>5.39 (0.8) | <br>-1.315<br>-1.350 | <br>.195<br>.181 |
| MetS<br>• Fasting glucose ≥ 100 mg/dl<br>• HDL-C < 40 mg/dl/< 50 mg/dl<br>• Waist circumference<br>• Blood pressure ≥ 130/85 mmHg<br>• Fasting triglycerides ≥ 150 mg/dl | 8 (21.6)<br>6 (16.2)<br>18 (48.6)<br>19 (51.4)<br>5 (13.5)<br>19 (51.4) | 14 (35.0)<br>3 (7.5)<br>10 (25.0)<br>10 (25.0)<br>7 (17.5)<br>13 (32.5) | 1.957<br>1.415<br>3.996<br>3.270<br>.935<br>2.812 | 1<br>.299<br>.058<br>.084<br>.497<br>.110 |
| Illness duration | 14.7 (9.5) | 16.2 (14.8) | -.493 | .624 |
| Overall antipsychotic exposition | 7.4 (9.0) | 8.1 (9.6) | -.172 | .864 |

*Cardiometabolic risk status by gender in the overall sample.*

frequency of MetS nor in the frequency of individual MetS criteria.

## Illness and treatment duration

Correlations between mean continuos cardiometabolic parameters and, respectively, duration of psychiatric illness and antipsychotic treatment exposure were not significant in the overall sample, nor in the subsample of subjects with duration of illness greater than 15 years (data not shown). In the subsample of subjects with less than 15 years of illness, significant correlations were found between the length of antipsychotic exposure and BMI ($r$ = .391; p = .024), waist circumference ($r$ = .481; p = .005), LDL cholesterol ($r$ = .519; p = .007) and fasting glucose ($r$ = .418; p = .019) (Table II).

## Discussion

In agreement with previous data, our sample of 77 patients with SMI, with an average of 15.5 years of

**Table II.** correlation between duration of psychosys and cardiometabolic risk.

| | Total Psychiatric Illness Duration | | | Cumulative Antipsychotic Treatment Duration | | |
|---|---|---|---|---|---|---|
| | N | pearson | p | N | pearson | p |
| BMI | 37 | .317 | .067 | 36 | .391 | .024 |
| Waist circumference | 37 | .396 | .025 | 36 | .481 | .005 |
| Blood pressure | | | | | | |
| Systolic | 37 | -.005 | .984 | 36 | .044 | .862 |
| Diastolic | 37 | .122 | .630 | 36 | .153 | .545 |
| Lipid metabolism | | | | | | |
| Total cholesterol | 37 | .165 | .366 | 36 | .279 | .129 |
| HDL | 37 | -.292 | .117 | 36 | -.160 | .408 |
| LDL | 37 | .364 | .062 | 36 | .519 | **.007** |
| Triglycerides | 37 | .074 | .686 | 36 | .024 | .898 |
| Carbohidrate metabolism | | | | | | |
| Fasting glucose | 37 | .314 | .080 | 36 | .418 | **.019** |
| $HbA_{1c}$ | 37 | .060 | .747 | 37 | .126 | .505 |

*Correlations between Mean continuos Cardiometabolic Health Parameters and duration of Psychiatric illness and antipsychotic treatment among subjects with less than 15 years of illness duration.*

mental illness duration and a 7.8 years of lifetime antipsychotic exposure, showed a pattern of increased smoking, overweight and MetS compared with the general Italian population [6-8].

Overall, almost half of the patients smoked tobacco (compared with a 21% rate in general population) [9] and way more than half were overweight. Rates of hypertension (17%), and diabetes (5.2%) were similar to those found in community samples, while the above 30% prevalence of MetS was dramatically higher compared to the general population. Our results are comparable with data deriving from other Italian clinical samples. Carrà et al. [10] found a 26% prevalence of MetS among individuals with SMI admitted to a University Hospital for inpatient treatment while Salvi et al. [11] found a prevalence of MetS as high as 25.3% among in- and outpatients with Bipolar Disorder referring to a University Psychiatric Clinic. Moreover, in the latter study high triglycerides, low HDL-C levels and high fasting glucose levels were observed in 34.7%, 32.3% and 11% of subjects, respectively. In a later study, the same research group found that MetS was present in about 21% of in- and outpatients with OCD [12] and was associated with greater duration of antypsychotic exposure.

Despite our results are quite consistent with previous studies, we are reporting the higher prevalence of MetS. A possible explanation might be that our sample included a big proportion of subjects with Schizophrenia spectrum or other psychotic disorders, that are arguably more disruptive of healthy lifestyles and/or socioeconomic status. In fact, body-composition alterations and other MetS components are likely to be mediated by the adoption of unhealthy lifestyles, such as poor diet, smoking and lack of exercise, related to these psychiatric conditions. On the other hand, the great prevalence in metabolic syndrome and overweight found in our sample might also be related to the exposure to antipsychotic agents. Salvi and colleagues [11], for example, reported that only 37% of subjects included were taking antipsychotics, compared with the 97% of our sample. However, our results are in keeping with a recent metanalysis of studies from different countries, reporting an overall rate of MetS among schizophrenic subjects of 32.5% [13].

Interestingly, while in the overall sample no correlations were found between individual cardiovascular risk factors and total duration of illness or overall exposition to antipsychotic treatment, body composition–related risk markers were significantly associated with longer total lifetime antipsychotic treatment duration and, to a lesser extent, to psychiatric illness duration in the subsample of patients with less than 15 years of illness. Similarly metabolic risk markers such as fasting LDL-C and fasting glucose were significantly associated with the overall mean treatment duration only in the subsample with shorter illness duration. Our findings confirm that antipsychotic drugs may closely impact weight-related risk factors during the first years of exposure, but also broad the putative critical period of 1-5 years after illness onset suggested by previous studies [14 15]. From this perspective, early stages of illness appear crucial both for

**Table III.** CVD risk assessment and management and members of the Community Mental Health team involved.

| CVD risk assesment (baseline, 6 months and yearly thereafter) | | CVD risk management | |
|---|---|---|---|
| **Family history** | **Nurse** | **Exercise classes** | **Occupational therapists** |
| BMI | Nurse | Diet and lifestyle advice | Nurse |
| Blood Pressure | Nurse | Smoking cessation | Psychiatric rehabilitation team |
| Fasting Glucose and Lipid Profile | Nurse | Liaison (dietist, cardiologist, diabetologist) | Psychiatrist |

the choice of one antipsychotic over another and for implementing prevention programs and timely interventions on cardiovascular risk of subjects with SMI. However, we cannot exclude that other covariates, such as familiar risk or antipsychotic dose, might also play a role in the risk of developing MetS.

The extent to which SMI, antipsychotic medications and unhealthy life-styles, including poor access to health services, individually contribute to cardiometabolic risk and to the development of MetS is still under debate [16 17]. Taken together, our findings are consistent with the hypothesis that the higher cardiometabolic risk of individuals with SMI depends on mental illness and consequent unhealthy lifestyle but also correlates with antipsychotic medications, especially in the first years of illness.

While interpreting our findings, several important limitations have to be acknowledged. First, the small study sample did not allow us to draw definitive conclusions. Moreover, the cross-sectional design of the study prevented us to clarify the exact temporal sequence between the onset of MetS (and individual cardiometabolic risk factors) and antipsychotic treatment initiation. Further, several confounding factors, such as different antipsychotic medications, familiar predisposition, socio-economic variables, might arguably have affected our results. On the other hand, our study has the strength of providing data collected under real life practice circumstances about cardiovascular health of severely ill patients. From this perspective, it is noteworthy that we included patients with no limitations with regard to illness duration or concurrent medical conditions, that are likely to be among exclusion criteria of most clinical trials.

Despite the above limitations, our study confirms the high cardiometabolic risk of individuals with SMI referred to an Italian Community Mental Health Service, showing an important relationship between this risk and early phases of antipsychotic treatment. Results from this study provide a framework for appropriate CVD risk assessment and management, that could be implemented in the Community Mental Health Service by adapting the existing manpower resources (Table III) and that will ultimately contribute to improve clinical outcomes related to CVD in persons with SMI.

## Take home messages for psychiatric care

- Related risk markers were significantly associated with longer total lifetime antipsychotic treatment duration and, to a lesser extent, to psychiatric illness duration
- Antipsychotic drugs may closely impact weight-related risk factors during the first years of exposure, but also broad the putative critical period of 1-5 years after illness onset
- Appropriate CVD risk assessment and management, that could be implemented in the Community Mental Health Service by adapting the existing manpower resources

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**Stefano Pallanti[1,2,3], Luana Salerno[4]**

[1] Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA), University of Florence, Florence, Italy;
[2] Department of Psychiatry and Behavioral Sciences, UC Davis Health System, Sacramento, CA, USA;
[3] Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, New York, NY, USA;
[4] Institute of Neurosciences, Florence, Italy

# ADHD: THE DARK SIDE OF EATING DISORDERS

**Abstract**

**Objectives:** Adult Attention Deficit Hyperactivity Disorder (ADHD) is a neurobiological disorder that is in most cases accompanied by other psychiatric conditions, and the latter often constitutes the reason for which adults seek professional help. Among ADHD co-occurrent conditions, Binge Eating Disorder (BED) has recently received more attention. However, there is evidence suggesting that ADHD may be a risk factor for developing not only binge eating behaviors but also other eating disorders, make them more difficult to treat with standard interventions. The aim of this review is to collect findings regarding the impact that an unrecognized and untreated ADHD may have on the onset of Eating Disorders (EDs), and explore the possibility that disordered eating may be another clinical feature of ADHD presentation.

**Materials and Methods:** For this aim, a PubMed search was conducted in June 17, 2016 for English-language publications from the previous 10 years. Search terms included: attention deficit hyperactivity disorder, ADHD, eating disorders, and comorbidity. Other articles have been obtained and included for their clinical and scientific relevance.

**Results:** Collected findings suggest that ADHD and EDs share some neurobiological and clinical features, and ADHD can predict the development of an ED. It may be possible that ADHD may foster the development of a particular form of ED that is more resistant to treatment and tends to relapse.

**Conclusions:** Implications of collected findings pertain to prevention of eating disorders in ADHD children and adolescents and in implementing appropriate treatment plans for adults with both ADHD and ED. Indeed, people with both ADHD and ED need specific treatment interventions, that target symptoms of ADHD and not only those of EDs. New evidence on the role of ADHD medications in the treatment of EDs has been also discussed.

**Keywords:** Attention deficit hyperactivity disorder, ADHD, Eating disorders, Comorbidity

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by severe and age-inappropriate levels of hyperactivity, impulsivity and inattention. The core symptoms of ADHD are present in approximately 5% of children and adolescents, with an over-representation of male subjects[1]. There is evidence showing that symptoms tend to persist over the lifespan in up to 50% of cases [2], leading to lower educational, occupational, social and clinical outcomes in adulthood [3]. ADHD is a heterogeneous disorder, and up to 70% of people affected present at least one comorbid psychiatric condition, increasing social and occupational distress [3].

Eating Disorders (EDs) consist in disordered eating behaviors characterized by a clinical as well phenotypic heterogeneity. DSM-5 made several changes to their classification, recognizing Binge Eating Disorder (BED) as a distinct condition, and modifing criteria for Anorexia (AN) and Bulimia Nervosa (BN) [4]. Moreover, DSM-5 included in the chapter "Feeding and Eating Disorders" some conditions usually diagnosed in

**Correspondence**

Stefano Pallanti
stefanopallanti@yahoo.it

the developmental age, i.e. avoidant/restictive food intake disorder, elimination disorder, pica and rumination disorder.
Among comorbid conditions of adult ADHD, mood, anxiety and substance use disorders are the most frequently reported. Despite some researchers suggested a central role of impulsiveness in causing bulimic and binge eating behaviors [5 6] and others described the presence of attention deficits in patients with AN or BN[7], up until now very little is known about the impact that unrecognized and untreated ADHD might have on the onset, course and treatment of EDs.
Some research findings demonstrated the presence of common personality traits between ADHD individuals and those with EDs [8], but the fact that ADHD is a disorder emerging early in infancy whereas EDs tend to present in adolescence and later in life may suggest that disordered or excessive eating behaviors can be, in some cases, another expression of the same disorder, that is ADHD. In this case, being ADHD a neurodevelopmental disorder, such particular form of ED could be more difficult to treat with standard interventions, because not targeting cognitive deficits ADHD-related.
Therefore, the objective of this review is to raise awareness of the potential presence of ADHD in some EDs, that may account for some difficulty in treatment and remission.

## Methods

PubMed was searched using the following combination of keywords: "Attention Deficit Hyperactivity Disorder" *OR* "ADHD*" AND* "Eating Disorders" *AND* "Comorbidity", published in English language in the last 10 years. The primary criteria for inclusion in this article were that each study had an adequate number of subjects, assessed symptoms using acceptable scales and tests, and was published during the past 10 years. Several older articles have been obtained from references and included for their scientific relevance to the aim of our paper.

## Results

We found only 53 articles published in the last 10 years matching keywords and inclusion criteria, that became 28 limiting results to papers regarding adult population. Collected findings have been integrated with evidence derived from older research studies, and results have been divided in the following sections: prevalence of comorbid ADHD and EDs, the nature of comorbid ADHD and EDs, neurobiological substrates of comorbid ADHD and ED. Aggregated data have been finally discussed, informing for clinical implications and indications for future research have been also provided.

### *Prevalence of Comorbid ADHD and ED*

Studies performed in women from the general population report a prevalence rate of 0.9% for Anorexia Nervosa (AN), of 1.5% of Bulimia Nervosa (BN) and of 3.5% of Binge Eating Disorder (BED) [9]. The vast majority of studies investigating the potential comorbidity between ADHD and ED reported higher prevalence rates: some studies found a prevalence of 11-16% of EDs (particularly Bulimia Nervosa) in people with ADHD [10-13], whereas ADHD has been found in 10-17% of subjects affected by AN purging type[14]. Previous studies [15 16] reported an increased tendency to binge in subjects with ADHD compared to controls and a prevalence of 8.3% for BED in ADHD individuals. However, other studies did not find increased ADHD rates in people with EDs [17 18].
There is evidence supporting a negative impact of ADHD on EDs. Biederman et al. [11] found that not only girls with ADHD presented a higher risk to develop an eating disorder, but in presence of both they experienced more mood, anxiety and disruptive behaviours in respect to those with only ADHD [11]. Data from this study showed females with ADHD to be 3.6 times more likely to suffer for an eating disorder compared to controls [11], and 5.6 times more likely to develop bulimia nervosa. Data from a nationally representative sample revealed that females had higher rates of comorbid ADHD and received more diagnoses of eating disorders than males (1.05% *vs* 0.20%, $p < .01$). Interestingly, in such study ADHD predicted the diagnosis of eating disorders in females but not in males [19]. These data are consistent with those by Davis et al. [20], who found childhood symptoms of ADHD to predict disordered eating in women aged 25-46 years [20], including BED.

### *The nature of comorbid ADHD and EDs*

It has been suggested that ADHD and EDs are linked by some neuropsychological features, such as varied degrees of impulsivity, low self-esteem as well deficits in attention and impaired executive functions [9 21 22].
A higher level of impulsivity in ED subjects than healthy people have been described in several studies [5 6], and a correlation between impulsivity and severity of BN [23 24] has been also noticed. Although

Stulz et al. did not find an association between the severity of ADHD symptomatology and the severity of EDs, they found a statistically significant correlation between the level of impulsivity and the avoidance of fattening food, and also excessive fasting [25]. The latter association was completely unexpected, being excessive control of caloric intake the tipical feature of AN patients. However, authors supposed that the excessive control on what AN subjects eat may work as a sort of protection by a primary impulsivity [25], and it could explain the frequently described "diagnostic flux" within EDs category [26], particularly between AN and BN [27 26].

The important role of impulsivity in comorbid ADHD and ED has been indicated also by Mikami et al. [28], when they found that childhood impulsivity predicted BN symptoms onset in adolescence. Such data have been recently confirmed by research showing people with clinical ADHD to be more prone to disordered eating, including binge/purge and restictive eating behaviour [29], whereas individuals with a subclinical ADHD were more prone to suffer from binge/purge behaviours and not from restrictive ones [30].

A recent study confirmed the role of cognitive deficits other than impulsivity in patients with BN: those with childhood ADHD not only presented more impulsivity than those with BN alone, as measured by the total BIS score, but they showed more inattentive symptoms on the BIS subscale "Attentional Impulsivity" [31 32]. Such results lead authors to suggest an additive effect of ADHD and BN with regard to impulsivity and inattention [31]. Attention and executive deficits (EF) have suggested to play a role in disordered eating in several ways: poor inhibitory control, poor planning and impaired self-monitoring – i.e. impaired executive functioning – may foster overeating even when not hungry and without caloric concerns [20 33], whereas attentional deficits may impede to adhere to a regular dietetic regime, because of the lack of attention to the internal signs of hunger as well satiety in individuals with ADHD [34]. Moreover, compulsive eating characterizing subjects with ADHD has been interpreted as a compensatory behaviour for controlling the frustration experienced for failures in organization [35].

However, other researchers emphasized the role of motivational or reward processing problems [36 37] in emerging and mainteinance of eating disorders. This perspective finds support in the fact that food is a natural reward, and palatable food stimulates bingeing by activation of the dopaminergic reward system [38], without concerns about consequences of such exagerated eating. The reward system has a key role also in ADHD [39] and together with impairments in EF, attention deficits and poor inhibitory control, it is considered another overlapping neurobehavioral factor underlying the frequent co-occurrence of ADHD and EDs.

The association between ADHD and obesity has been more studied. Evidence shows that ADHD is a risk factor for obesity [40 41]: it has been found in 25% of treating seeking obese individuals [42], and in a 33-year follow-up study males with ADHD resulted 2 times more likely to become obese than controls [43]. However, it would be noted that binge eating behaviors are frequent in obese patients, and that overweight – as well BN and binge eating – is more frequent in people with ADHD than in the general population [20 31 33].

### *Neurobiological substrates of comorbid ADHD and ED*

Data from neuroimaging and pharmacological studies show some shared neurobiological substrates which can give us some insights about the link between ADHD and EDs.

An explanation for comorbid ADHD and ED, particularly BED, may be found in the so-called Reward Deficiency Syndrome. The Reward deficiency syndrome is characterized by reward-seeking behavior, and it is caused by genetic variations leading to insufficient numbers of D2 receptors in the brain of people carrying the D2A1 allele. A dysfunction in DRD2 and DRD4 underlying a reward deficiency system [44-46] has been described for both ADHD [47-49], and obese people with altered eating behaviours [50-54].

We know from accumulated evidence that the cognitive deficits associated with ADHD emerge from dysfunctions particularly in fronto-striatal or mesocortical brain networks, and the alterations in reward processing have been attributed to dysfunctions in the mesolimbic dopaminergic system [37 55]. Interestingly, FMRI studies performed on adults with BN and BED also demonstrated the presence of a dysfunctional frontostriatal circuitry, responsible for self-control and impulsive behaviors [56 57], and a decreased recruitment of reward pathways in patients with persistent binge eating episodes even after treatment [58]. However, these studies did not take into account comorbid ADHD and EDs, although such investigation would be of value.

The fundamental role of dopamine (DA), as well norepinephrine (NE) systems in regulating eating behavior and reward [59 60] have been also confirmed by findings from a recent neuroimaging study, using the administration of methylphenidate in order to amplify the signals of dopamine, and showing that

food stimuli significantly increased DA in the caudate and putamen in obese subjects with BED, but not in those without BED [61]. In another study performed on subjects with BN using PET, the striatal dopamine release resulted associated with the frequency of binge eating [62]. However, in this case it is not possible to exclude the presence of an undiagnosed ADHD and its influence in such findings.

Studies on animal models suggested an involvement of alterations in the brain derived neurotropic factor (BDNF) in the relationship between ADHD and binge eating. Indeed, altered BDNF was found to cause excessive food intake in mice, as well impairments in impulse control and a tendency to become obese [63-65]. However, findings from animal models need caution to be interpreted, and generalization to humans is not possible.

It would be noted that there is some discordance about the association between severity of ADHD and severity of ED, with some studies indicating no association [25], and others finding a positive one between eating episodes and ADHD symptoms [66]. This discordance suggests the presence of other factors that could mediate the ADHD-ED interconnection. Depression may be one of them [67], and also disordered sleep may exert an effect. Indeed, disordered sleep patterns and daily sleepiness have been found associated to unhealthy eating habits leading to overweight and obesity, fostering unhealthy food consumption behaviours in children [68 69]. In this line of research, interestingly a link between disrupted circadian rhythm and obesity has been recently proposed in adults with ADHD [70]. This finding gives support to what previously suggested by Cortese and colleagues [33 71], who indicated an involvement of the hypocretin/orexin pathways in the relationship between eating, sleep and ADHD. Even though the orexin system has recently received increased attention for its importance in the regulation of emotion, reward, and energy homeostasis [72], its role in comorbid ADHD and EDs needs specific investigation.

## Discussion

We believe that there is enough evidence supporting the existence of shared neurobiological underpinnings explaining the frequent presence of EDs in ADHD. Less is still known regarding the presentation of ADHD in EDs patients and its impact change to EDs emergence and maintenance. It has been largely reported how people with EDs feel embarassement, sense of guilt, depression and a sense of weakness which makes them less likely to ask for help. This is the reason for which binge eating disorder (BED) is frequently unrecognized, and it is more frequently treated when it is associated with obesity. However, as Cortese and colleagues [33] pointed out, such feelings of frustration and ineptitude frequently derives by the core deficits of ADHD, and are usually reported by adults affected by the disorder. People with ADHD suffer from their problems to persist toward goals, for their difficulty to inhibit their actions even when these may compromise their desired goal. Such features led Barkley to define ADHD as a disorder of self-regulation [73], and such impaired capacity to regulate own behavior is also a reported characteristic of people with BN and BED [74]. Evidence shows that ADHD-related deficits may create obstacles in adhering to a dietetic regime [43], and this is confirmed by recent data reporting ADHD as the main cause of treatment failure in refractory obesity candidates for bariatric surgery [75].

We believe that screening for ADHD symptoms individuals with disordered eating may help clarify difficulty in ED management and may offer new treatment options. Recent pharmacological reports suggested that ADHD medications, by acting on the brain areas involved in both ADHD and EDs, can improve not only attention and impulsive behavior but also abnormal eating [35 43 76-78]. Interestingly, recently the stimulant lisdexamfetamine (LDX) has been approved by FDA as the first medication indicated to treat moderate to severe BED in adults [79]. The rationale of its use relies on accumulated evidence of the already reported dysfunction of the dopamine (DA) and norepinephrine (NE) systems in binge eating, and in this context LDX resulted effective in facilitating DA and NE neurotransmission, and consequently in reducing pathological excessive eating [80].

The potential benefit of ADHD medication for disordered eating is not a new thing, being already suggested years ago, when Meredith et al. [81] found that the repeated amphetamine administration increased BDNF expression in the rat amygdala, piriform cortex and hypothalamus, targeting those brain pathways that are impaired in EDs. Methylphenidate resulted effective in reducing sugar craving and consequently bingeing in several studies [82-84], whereas the non-stimulant atomoxetine demonstrated positive effects on weight control in obese women [85]. By acting on noradrenergic synapses, atomoxetine showed its effect by reducing binge eating and promoting weight loss also in adults with BED [85].

Taken together all findings seem to confirm that the

presence of ADHD may influence EDs presentation, its response to treatment and also relapse. It seems the people with ADHD and ED present a double impairment because they are affected by more cognitive deficits influencing their emotional status. For this reason, people with both ADHD and ED need specific treatment interventions, targeting those symptoms of ADHD which usually are not considered in the treatment of only ED. Pharmacological intervention should consider the recent evidence regarding the effectiveness of ADHD medications in disordered eating, and need to be complemented by other non-pharmacological treatments, as psychoeducation, CBS and coaching, in order to improve those areas – attention, planning, organization, emotional control – that constitute the dysfunctional core of ADHD for facilitating the attainment of target goal, as well mainteinance of results.
Current evidence cannot exclude what we suggested, i.e. the existence of a particular subtype of ED that is expression of cognitive deficits of ADHD, and not a simple co-morbid condition. Such hypothesis finds some support in data from Fernandez-Aranda and colleagues [66] showing a different severity of ADHD among ED subtypes. Specifically, it has been found a more severe ADHD in people with BN, BED and EDNOS and a lower prevalence of ADHD in the AN group. Authors explained such findings as the expression of the common impulsivity trait characterizing ADHD and BN/BED individuals, whereas AN subjects were less affected by ADHD symptoms because of their rigidity and perfectionism, that did not match with an ADHD profile. However, it should be noted that this interpretation does not take into account the frequent diasgnostic switches of people with EDNOS (currently divided into the Other Specified Feeding or Eating Disorder or OSFED, and Unspecified Feeding or Eating Disorder or UFED) among EDs diagnostic categories. Additionally, perfectionism has been also reported in adult ADHD, as a coping strategy to overcome mental chaos [86].
It would be noted that the vast majority of reported studies present some limitations that need to be taken into account. Main limitations are the different population studied and diagnostic instruments used, many of them did not differentiate between a diagnosis of ADHD and the solely presence of symptoms of ADHD, and they usually lack of a control group. Therefore, future research should address these limitations with adequate methodology, using control groups and investigating the role of potential mediating factors.To test our hypothesis, longitudinal and perspective studies are needed.

From a clinical point of view, our review indicate how can be of value the clinical assessment of ADHD in patients with EDs, particularly in females seeking help, in light of evidence showing that girls and women are three times more likely to be treated for depression before receiving ADHD diagnosis [13].
In presence of both ADHD and ED, it should be necessary to treat ADHD first, in order to normalize those cognitive dysfunctions, such as executive deficits, impaired attention, poor impulse and emotional control, that otherwise will hamper effectiveness of treatment. New evidence from pharmacological studies reporting ADHD medications effective in people with EDs should be also considered, as well the implementation of those psychological intervention that resulted effective in ADHD individuals, because aimed to improve those executive functions (planning, organizing, control of behavior) that are compromised by the presence of such disorder.

## Conclusion

In summary, aggregated evidence shows that ADHD may be a potential risk not only for binge eating, but for all EDs as well for obesity. Data from neuroimaging and pharmacological studies have given new insight on shared neurobiological underpinnings which may explain the link between ADHD and EDs, and indicate new treatment options. Clinicians should be aware of the higher prevalence of ADHD in EDs, and screen for the presence of the disorder in order to implement more efficacious interventions, by targeting those cognitive deficits characterizing people with ADHD, which if not recognized could compromise treatment results. Up until know, there are still few studies investigating comorbid ADHD and EDs, and available data cannot exclude the presence of a different subtype of ED, that may emerge in life as another clinical expression of untreated ADHD, and that is for this reason more resistant to standard treatments. Further research is needed to explore this possibility, by comparing individuals with both ADHD and EDs and comparing them with subjets affected by only ADHD or ED and matched controls. In the meanwhile, in light of the evidence indicating ADHD to be a predictor of EDs and obesity, prevention programs in ADHD population should be implemented, whereas pharmacological and non-pharmacological treatments generally proposed for adult ADHD should be considered in EDs management.

## Take home messages for psychiatric care

- ADHD and EDs share some neurobiological features
- Evidence shows that ADHD can predict the development of ED
- Because of its earlier onset and cognitive deficits, ADHD may foster the development of a more resistant form of ED, and causes the relapse
- New evidence shows efficacy of ADHD medications in the treatment of EDs
- Clinicians should assess for the presence of ADHD individuals with EDs and obesity
- Future research is needed for the implementation of more targeted intervention

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**Emilio Sacchetti**[1,2,3], **Antonio Vita**[2,3,4]

[1] University Psychiatric Unit No. 22, Brescia University School of Medicine and Brescia Spedali Civili, Brescia, Italy; [2] Department of Clinical and Experimental Sciences, Neuroscience Section, University of Brescia, Brescia, Italy; [3] Department of Mental Health, Spedali Civili Hospital, Brescia, Italy; [4] Psychiatric Service, Department of Mental Health, Brescia University and Brescia Spedali Civili, Brescia, Italy

# ORAL LURASIDONE FOR PEOPLE WITH SCHIZOPHRENIA: CLINICAL PRACTICE RECOMMENDATIONS EMERGING FROM A REVIEW OF THE LITERATURE

**Abstract**

Lurasidone, a benzisothiazol derivative of azapirone, is a second-generation antipsychotic that couples antagonist activity on $D_2$ and 5-hydroxytryptamine 2A ($5HT_{2A}$) receptors with potent antagonist and partially agonist effects on $5HT_7$ and $5HT_{1A}$ receptors, respectively. Furthermore, behavioural studies in animals show that lurasidone not only has antipsychotic activity but also has possible antidepressant and procognitive properties. Initially approved by the US Food and Drug Administration for the treatment of people with schizophrenia, lurasidone has received the same indication in Europe and other countries, and has also been approved in the United States and Canada for the treatment of the episodes of major depression associated with bipolar I disorder. Based on MEDLINE citations supplemented by hand-searched publications, this review addresses the issue of the short-term and long-term efficacy and tolerability of lurasidone, as it emerges from the international literature. A sufficient body of evidence strongly supports the conclusion that lurasidone may be included among the first-line options for the pharmacological treatment of patients with schizophrenia because it provides good antipsychotic efficacy and a safety and tolerability profile that is benign in general or even, as in the case of the cardiometabolic effects, almost neutral. Future comparisons with other antipsychotic medications are however indicated to promote awareness of the use of lurasidone in psychiatric services. Further studies are also warranted to validate the early clinical expectations that lurasidone has the antidepressant and procognitive properties predicted by animal studies and to show that it is cost-effective not only in probabilistic models but also in the routine treatment of patients with schizophrenia.

**Key words:** Lurasidone, Schizophrenia

## Introduction

Antipsychotic medications remain the milestone in the therapy of schizophrenia [1 2] and second-generation antipsychotics represent an improved standard of care in comparison with first-generation antipsychotics [3-6]. Nevertheless, the prognosis of the disorder continues to be far from good. Even when correctly treated, people with schizophrenia are commonly affected by residual symptoms, present tangible impairments in almost all areas of functioning, have a poor quality of life, show an excess of mental and physical comorbidities, and are subject to evident health care inequalities, with a mortality rate from both natural and unnatural causes [7-28]. This long chain of unfavourable events inevitably reverberates with

**Correspondence**

Emilio Sacchetti
emilio.sacchetti@unibs.it

dramatic consequences on the familial network of the patient, the wider society, and the health care system in general [17 29-36]. Therefore, interventions that can mitigate this multifaceted burden are required.

The acquisition of new antipsychotics can satisfy this need provided that they are not mere copies of medications already on the market but really shown distinctive and improved effectiveness. Starting from these considerations and in light of the widespread and increasing use of lurasidone in daily psychiatric practice in many countries, a systematic review on its efficacy and tolerability in the treatment of patients with schizophrenia is indicated to promote awareness of this medication among clinicians.

## Lurasidone market

Like ziprasidone, lurasidone hydrochloride is a benzisothiazol derivative of azapirone with a unique pharmacokinetic and pharmacodynamic profile among second-generation antipsychotics [37-42].

In the last few years, lurasidone has received regulatory approval for the treatment of people with schizophrenia by national agencies including the US Food and Drug Administration, Health Canada, Swiss Medic, Australian Therapeutic Good Administration, and the European Medicine Agency. Analogous to other antipsychotic medications, lurasidone has also received approval from the US Food and Drug Administration and Health Canada for the treatment of depression in patients with bipolar I disorder.

## Dosage

According to the product labelling [43], the recommended dose range for lurasidone for the treatment of schizophrenia is 40–160 mg/day. According to a positron emission tomography $D_2$ occupancy study [44], 65% $D_2$ receptor occupancy seems to be required to achieve improvement in positive symptoms. No association between receptor occupancy and improvement in negative symptoms was instead observed. The study had however a small sample size.

Lurasidone is commercialized in tablets of 20, 40, 80 and 120 mg [43]. Based on its pharmacokinetics, metabolism, and bioavailability [41 45-47], lurasidone must be taken once daily with food. A relevant reduction in bioavailability when the medication is consumed under fasting or quasi-fasting conditions [43 46 47] means that lurasidone must be taken with a meal of at least 350 kilocalories. This indication mimics ziprasidone, although at a lower caloric threshold [48-51]. With meals exceeding the minimum of 350 kilocalories, neither the absolute calorie count nor the fat content have been reported to have a relevant impact on the magnitude of the food effect of lurasidone [41 43 46].

In general, an initial dose titration is not required and the recommended starting dose is 40 mg/day. However, in patients with renal or hepatic impairment and when modest CYP3A4 inhibitors are co-administered, a starting dose of 20 mg and a maximum dose of 80 mg are indicated [41 43 52]. No evidence on the need for dose adjustments in elderly patients have emerged to date [45]. Some prudence is recommended with undernourished individuals because lurasidone is highly protein bound, with a special affinity for albumin and alpha-1 glycoprotein [45].

## Literature selection

To identify the literature pertinent to the efficacy and tolerability of lurasidone in the treatment of patients with schizophrenia, MEDLINE citations up to August 31, 2015 were surveyed using the National Library of Medicine's PubMed online search engine, with the keyword 'lurasidone' in combination with 'schizophrenia'. The search was restricted to papers written in English and published in peer-reviewed journals. Double-blind and open-label trials, post hoc and pooled analyses, observational and simulation studies, reviews, and meta-analyses were considered suitable for a first, rough evaluation. The references in all the articles retrieved were hand-searched for supplementary material together with other articles found independently. To be considered in the review, the results had to be explicitly reported with sufficient details on statistical procedures.

Overall, the literature search generated 57 references. After a first inspection, 35 reports identified as reviews, duplications, insufficiently detailed or nonpertinent were excluded (Fig. 1). The remaining 22 publications included in the review reported results relative to 11 original trials and 3 extension studies (Fig. 2).

The results of the various reports have been organized into 2 main sections, one devoted to efficacy and the other to safety and tolerability, each with supplementary subdivisions in relation to the study design. A third section relative to the potential impact of lurasidone on health care costs of schizophrenia is also included.

## Short-term efficacy

The short-term efficacy of lurasidone in patients with schizophrenia has been directly challenged in 5 dedi-

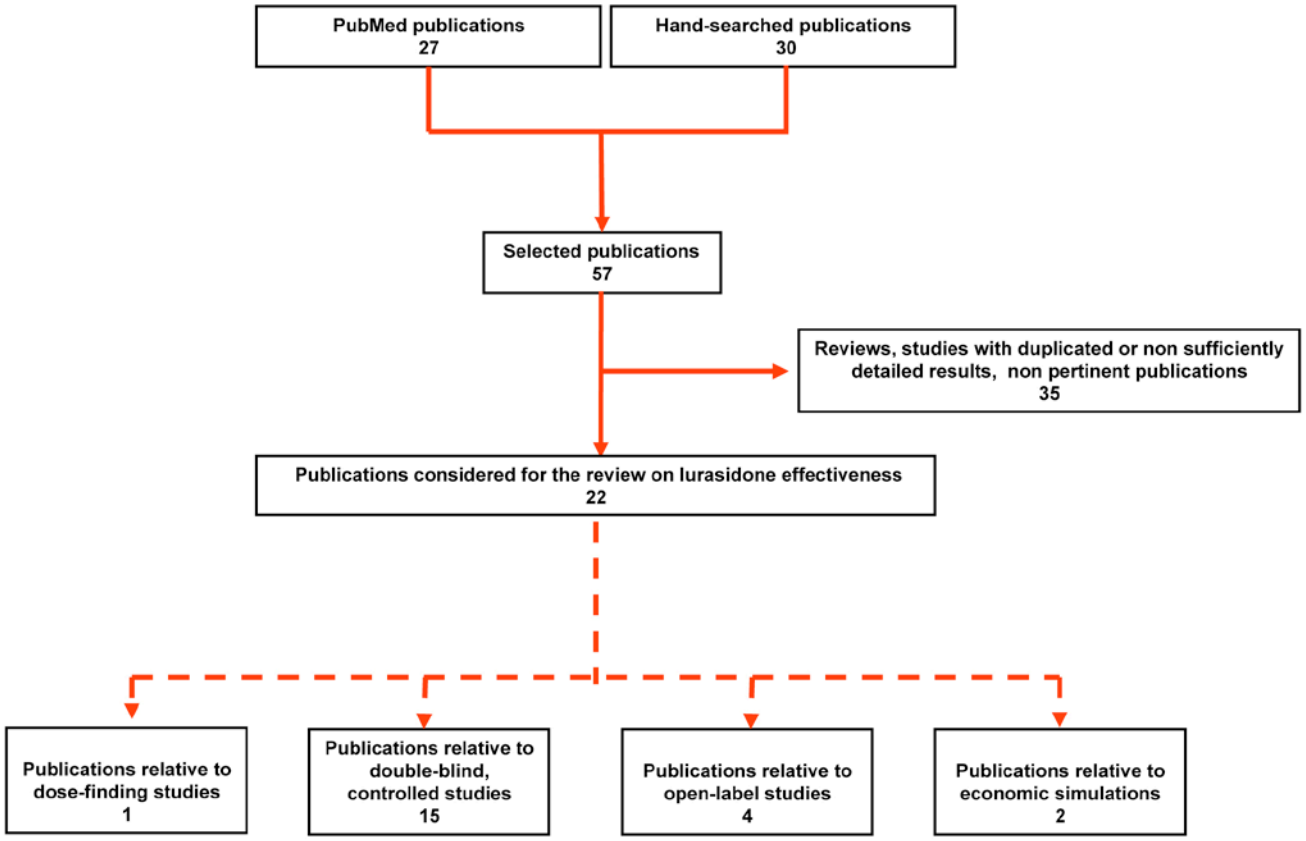


FIGURE 1.

Search strategy used to identify the clinical studies to be included in the review on the effectiveness of lurasidone. The solid, red lines link the steps from the identification of all the available publications to those used in the review. The dashed red lines link the subdivisions of the studies valid for the review, according to the study design.

cated double-blind, placebo-controlled, randomized clinical trials (RCTs), 1 RCT with an active comparator, and 1 open-label switch study.

The literature [52-54] also cites an unpublished, double-blind, randomized, phase 2 trial. This study compared lurasidone, at fixed doses of 20, 40, and 80 mg/day, with a placebo and included a supplementary haloperidol 10 mg arm for assay sensitivity. The results for lurasidone and haloperidol were no different from the placebo. However, this finding was not supported by explicit, detailed, quantitative analyses and thus the trial was not included in the review.

A double-blind, 8-week, dose-response trial [55] demonstrated the superiority of 40 and 80 mg of lurasidone in comparison with 20 mg. However, the study did not include any comparison with placebo or an active comparator and was therefore considered not eligible for inclusion in this review on the short-term efficacy of lurasidone.

***RCTs versus placebo***

Among the 5 published short-term RCTs versus placebo, 2 also included a supplementary group randomized to another second-generation antipsychotic medication. This third arm was in response to the need to carry out sensitivity analyses when the primary outcome measure failed to separate lurasidone from placebo. Direct comparisons between lurasidone and these potential comparators were precluded because the sample was not adequately powered for this purpose.

The results of one RCT were reported in 2 independent publications. The oldest, double-blind RCT [56] was a phase 2 study conducted in 16 sites in the United States that challenged, over a 6-week period, the efficacy of 2 fixed doses of lurasidone, 40 and 120 mg/day, in a sample of patients who satisfied the DSM-IV criteria for schizophrenia and were hospitalized for a psychotic exacerbation. After a screening period of up to 14 days and a single-blind placebo washout period of up to 7 days, the sample population was randomized on a 1:1:1 ratio to lurasidone 40 mg ($n$ = 50), lurasidone 120 mg ($n$ = 49) or placebo ($n$ = 50). The lurasidone 40 mg group received the target dose from the first day of treatment, whereas the patients in the lurasidone 120 mg group started with an ini-

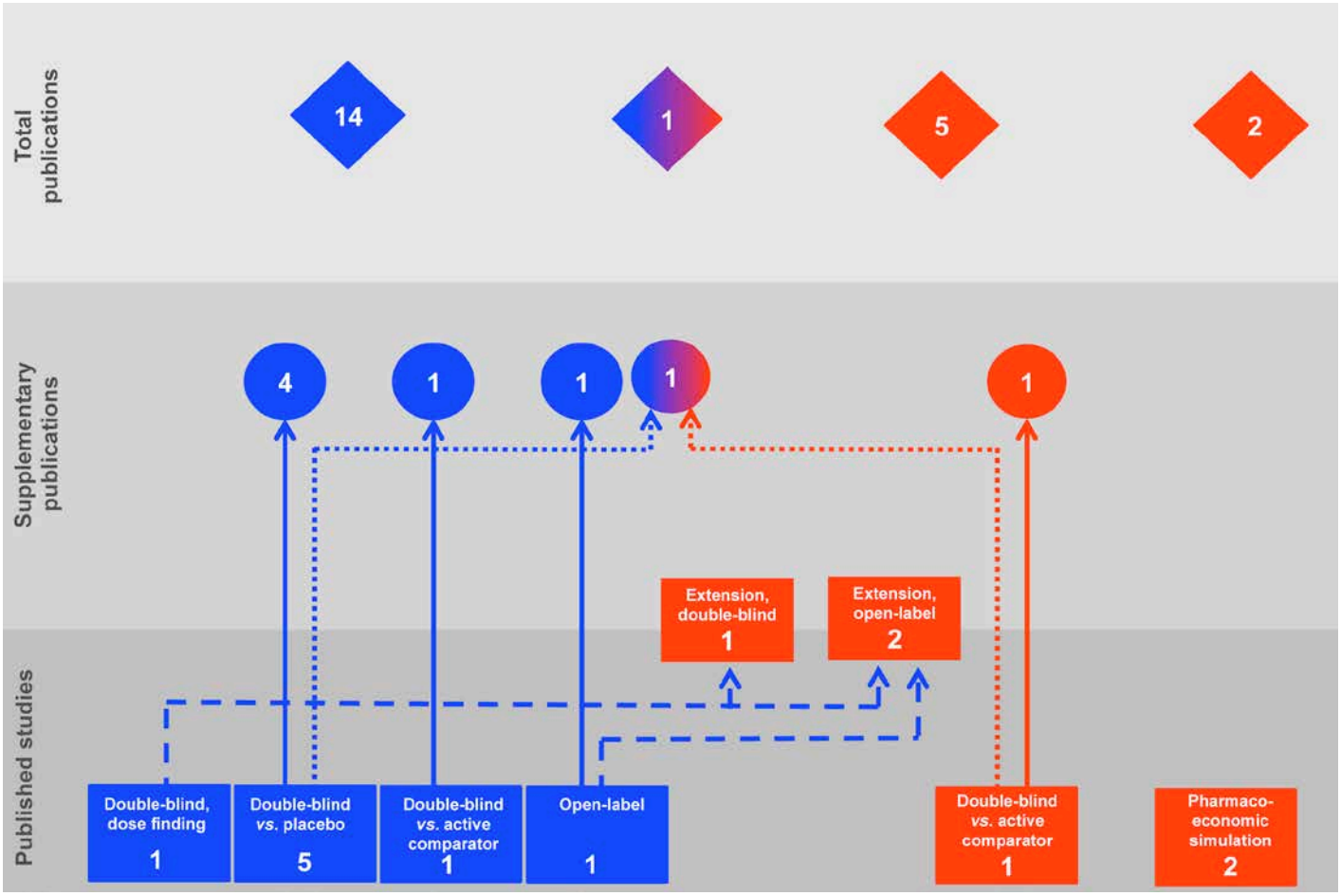


FIGURE 2.

Process linking the experimental studies with publications. Blue: publications on short-term studies; red: publications on long-term studies; blue and red: publications on short- and long-term studies; solid lines: link published, original studies with supplementary publications; dashed lines: link original studies with extension studies; dotted lines: link short- and long-term trials involved in supplementary publications. PBO: spell out.

tial dose of 40 mg/day that was increased to the target dose by day 6. The primary outcome measure was represented by the change from the baseline score after 6 weeks for the Brief Psychiatric Rating Scale (BPRS) [57]. The changes at the end point from the baseline scores relative to the total Positive and Negative Syndrome Scale (PANSS) [58] and the positive, negative, and general psychopathology PANSS subscales acted as secondary efficacy measures together with the Clinical Global Impression of Severity (CGI-S) and the Clinical Global Improvement (CGI-I) scales [59]. The data were collected on a last observation carried forward (LOCF) basis. The statistical approach involved analysis of covariance and the Cochran-Mantel-Haenszel test. On the basis of the change in baseline BPRS score, both the lurasidone groups showed greater improvement than the group randomized to placebo (Table I). The Cohen effect size of the change in BPRS score at the end point was 0.53 and 0.65 for the lurasidone 40 mg and 120 mg groups, respectively. At the same 6-week visit, only patients in the lurasidone 120 mg group showed improvements from baseline scores in total PANSS, PANSS positive, negative, and general psychopathologic subscales, CGI-S, and CGI-I. Patients randomized to lurasidone 40 mg did not differ from patients in the placebo group with regard to the same secondary efficacy measures. A second, US, multicentre, parallel-group, double-blind, placebo-controlled trial [60] carried on in 22 sites involved patients with DSM-IV schizophrenia hospitalized for an acute exacerbation of psychotic symptoms and to assess the 6-week efficacy of a fixed dose of lurasidone (80 mg). After a 7- to 14-day screening period and a 3-to 7-day placebo washout interval, 180 patients were randomized to lurasidone 80 mg or placebo, in a 1:1 ratio. The therapy was administered in a once-daily morning dose, with or immediately after breakfast. The BPRS derived from the PANSS, the PANSS, the CGI-S, and the Montgomery-Äsberg Depression

**Table I.** Short-term RCTs *vs.* placebo. Efficacy at the endpoint.

| Study | Duration (weeks) | Lurasidone dose (mg/day) | BPRS | Total PANSS | PANSS positive subscale | PANSS negative subscale | PANSS general subscale | PANSS cog nitive subscale | CGI-S | CGI-I | MADRS | NSA-16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ogasa et al. 2013 [56] | 6 | 40 | ◆ | ● | ● | ● | ● | | ● | ● | | |
| | | 120 | ◆ | ◆ | ● | ● | ● | | ● | ● | | |
| Nakamura et al. 2009 [60] | 6 | 80 | ◆ | ◆ | ● | ● | ● | ● | ● | | ● | |
| Meltzer et al. 2011 [62] | 6 | 40 | | ◆ | ● | ● | ● | ● | ● | | ● | ● |
| | | 120 | | ◆ | ● | ● | ● | ● | ● | | ● | ● |
| | | 40 | | ◆ | ◆ | ◆ | ◆ | | ◆ | | ◆ | ● |
| Nasrallah et al. 2013 [63] | 6 | 80 | | ◆ | ● | ● | ● | | ● | | ● | ● |
| | | 120 | | ◆ | ● | ● | ● | | ◆ | | ◆ | ● |
| Loebel et al. 2013 [68] | 6 | 80 | | ◆ | ● | ● | ● | | ● | | ● | ● |
| | | 160 | | ◆ | ● | ● | ● | | ● | | ● | ● |

◇: *primary efficacy measure;* ●: *secondary efficacy measure; green: lurasidone significantly better than placebo at the 6-week endpoint; red: no lurasidone/placebo difference at the 6-week endpoint; gold: trend for lurasidone to be better than placebo at the 6-week endpoint.*
*BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Inventory-Severity; CGI-I: Clinical Global Inventory-Improvement; MADRS: Montgomery-Åsberg Depression Rating Scale; NSA-16: 16-item Negative Symptom Assessment.*

Rating Scale ( MADRS) [61] were used to define symptom improvement. The change in the BPRS at the end point from the baseline score represented the primary outcome measure. The statistical package included two-way analysis of covariance of the LOCF data, and the Cochran-Mantel-Haenszel test. At the end point, the improvement in the BPRS of the lurasidone arm was superior compared with that found in the placebo group (Table I). The change in the BPRS from baseline separated lurasidone from placebo by day 3 and thereafter. At the end point, the Cohen effect size for the improvement in the BPRS was 0.39. The superiority of lurasidone in comparison with placebo also emerged when the positive, negative, general and cognitive PANSS subscales, the CGI-S, and the MADRS were considered. A subanalysis relative to patients with a baseline score of at least 12 was also performed because the total sample population had a relatively low mean baseline MADRS score. Lurasidone was confirmed to be superior in comparison with placebo and the effect size relative to the total sample increased from the 0.37 for the total sample to 0.44 for the subgroup with a baseline MADRS score of 12 or more.

Another international, 6 week, parallel-group, double -blind trial [62] carried on in the United States, Colombia, Lithuania, and Asia compared 3 fixed doses of lurasidone with placebo. In order to make a sensitivity assay possible, the trial also included a group exposed to a fixed dose of olanzapine. Adult patients with a DSM-IV diagnosis of schizophrenia who were hospitalized for an acute exacerbation of their psychosis were randomized on a 1:1:1:1 ratio to lurasidone 40 mg ($n$ = 119), lurasidone 120 mg ($n$ = 118), placebo ($n$ = 114), or olanzapine 15 mg ($n$ = 122). The antipsychotics were taken in the

morning with a meal or within 30 minutes after eating. In the 3 lurasidone arms, the initial lurasidone dose corresponded to the target dose. Patients assigned to olanzapine received 10 mg during the first week of treatment and the target dose thereafter. The assessment of efficacy was based on PANSS, CGI-S, and MADRS. The primary outcome measure was the change from baseline PANSS total score at the end of the 6 weeks of treatment. The statistical plan implied the use of mixed models for repeated measurements with an unstructured covariant matrix, analyses of covariance and logistic regression analyses. At the 6-week end point, the reduction from the baseline PANSS total score was significantly greater for each lurasidone arm compared with the sample randomized to placebo (Table I). The Cohen effect sizes relative to the 6-week improvement in PANSS total score were 0.43 and 0.26 in the case of the lurasidone 40 mg and 120 mg groups, respectively. The change from baseline in PANSS total score separated placebo from lurasidone 40 and 120 mg from the first and the third week of treatment, respectively. At the same end point, the results for the 2 lurasidone groups were better than placebo in relation to an extensive list of secondary efficacy measures that included the PANSS positive, negative, general, and cognitive subscales, the CGI-S, and the MADRS. The olanzapine 15 mg group was separated from the placebo group from the first week of treatment.

An international, multisite, 6-week, double-blind, placebo-controlled trial of inpatients with an acute exacerbation of DSM-IV schizophrenia [63] randomized in a 1:1:1:1 ratio to lurasidone 40 mg (*n* = 125), 80 mg (*n* = 123), 120 mg (*n* = 124) or placebo (*n* = 128) after tapering off psychotropic medications and a single-blind placebo run-in period. Depending on the treatment assignment, patients received 1 lurasidone 40 mg tablet and 2 matching placebo tablets, 2 lurasidone 40 mg tablets and 1 matching placebo tablet, 3 lurasidone 40 mg tablets, or 3 matching placebo tablets. The tablets were taken together in the morning, within 30 minutes after a meal. Patients randomized to 40 or 80 mg of lurasidone received the target dose from the first administration, whereas those entered in the lurasidone 120 mg arm were treated with 80 mg in the first 3 days. The efficacy was assessed using the PANSS, the CGI-S, and the MADRS. The change from the baseline PANSS total score at the end point represented the primary outcome measure. The statistical approach included a mixed model for repeated measurements with an unstructured covariance matrix and analysis of covariance. At the end point, only patients randomized to lurasidone 80 mg reached a greater improvement in baseline PANSS total score than individuals receiving placebo (Table I). The reduction from the baseline total PANSS score separated lurasidone 80 mg from placebo from the second week of treatment to the end point. For the secondary efficacy measures, lurasidone 80 mg was better than placebo relative to improvement at the end point from the baseline scores in the PANSS positive subscale and CGI-S. At week 6, no lurasidone/placebo difference was found in the lurasidone 40 mg group and only a reduction in the PANSS positive subscale emerged in patients randomized to lurasidone 120 mg. The negative results relative to the lurasidone 40 and 120 mg groups could be at least partially attributed to the relevant improvement that characterized the placebo arm. In the presence of strong placebo effects, statistical significance may be reached in samples, like the lurasidone 80 mg group, characterized by an appreciable reduction in symptoms but not when the sample population, as in the lurasidone 40 and 120 mg arms, showed a less pronounced treatment response. Recent demonstrations [64-67] that placebo-controlled trials of schizophrenia have resulted in a significant loss of significance concomitant with an evident increase in the placebo responses support this proposal.

In a 6-week, fixed-dose, double-blind trial [68] carried out at 63 sites in North and South America, East Europe, and India, 496 adult inpatients with a DSM-IV-TR diagnosis of schizophrenia and an acute exacerbation of psychotic symptoms were randomized to receive in the evening, with a meal or within 30 minutes after eating, lurasidone 80 mg (*n* = 125), lurasidone 160 mg (*n* = 121), or placebo (*n* = 121). A group of 119 patients was randomized to quetiapine XR 600 mg. This arm was indicated for sensitivity analyses but not for direct comparisons with lurasidone. After a screening period of 14 days or less to taper off psychotropic medications, the patients completed a 3- to 7-day placebo washout period and were randomized in a 1:1:1:1 ratio to one of the 4 treatment arms. Individuals randomized to lurasidone 160 mg or quietapine XR 600 mg started at a dose of 100 or 300 mg/day and reached the target dose after 2 days. At the screening evaluation and thereafter at predefined time intervals, the patients were evaluated with an extended battery of scales that included PANSS, CGI-S, MADRS and the Negative Symptom Assessment Scale (NSA-16) [69]. Other measures relative to the quality of well-being, satisfaction with medication and quality of sleep were also assessed. The 6-week

change from baseline in PANSS total score acted as the primary outcome measure. Linear models for repeated measures with an unstructured covariance matrix, logistic regression analyses, and analyses of covariance were used for the statistical analyses. The mean change at the end point from baseline total PANSS score was -22.8 and -26.5 for the lurasidone 80 mg and 160 mg group, respectively. These improvements were remarkably superior to the –10.3 observed in the placebo group (Table I). The Cohen effect size was 0.58 for the lurasidone 80 mg group and 0.83 for the lurasidone 160 mg arm. The changes in PANSS total score from baseline separated the 2 lurasidone groups from the placebo group from the fourth day of treatment. Compared with the placebo group, the 2 lurasidone arms showed better improvement in all the secondary efficacy measures. The arm treated with quetiapine XR 600 mg was equally superior to placebo in both the primary and secondary efficacy measures. The patients enrolled in this core trial were also evaluated for cognitive performance and functional capacity [70]. Using the CogState computerized cognitive battery [71] and the University of California San Diego Performance-based Skills Assessment Brief (UPSA-B) [72]. When the full sample population was entered in the analysis, the changes from baseline to the 6-week end point in the neurocognitive composite Z score did not separate the 2 lurasidone groups from the samples randomized to placebo or quetiapine XR. When the analysis was restricted to the evaluable sample (*n* = 267) consisting of 267 participants, lurasidone 160 mg was superior to placebo and quetiapine XR 600 mg. In turn, the 6-week changes from baseline in UPSA-B total score showed that the patients randomized to lurasidone 80 mg, lurasidone 160 mg or quetiapine XR 600 mg acquired superior functional capacity in comparison with those in the placebo group.

***RCTs versus an active comparator***

Only one short-term study of lurasidone against an active comparator has been carried out so far. This randomized, 3-week, double-blind, fixed-dose, parallel-group, double-dummy trial involved 33 US sites and compared lurasidone with ziprasidone in clinically stable patients who met the DSM-IV criteria for schizophrenia or schizoaffective disorder. The trial had safety as the primary outcome rather than efficacy. Initially, the patients were tapered off any psychotropic medication and underwent a 1- to 3-day placebo run-in washout period. Thereafter, they were randomized in 1:1 ratio to lurasidone 120 mg (*n* = 154) or ziprasidone 160 mg (*n* = 153). The therapy was administered on a twice daily basis. In particular, the lurasidone group started at a dose of 80 mg and reached the target dose on day 4, receiving the active capsule in the morning and an identical placebo capsule in the evening. In turn, the ziprasidone group started at 40 mg twice daily and on day 4 this was increased to 80 mg twice daily. The trial had been subject of 2 independent publications [73 74]. In the first core publication [73], the improvements relative to the PANSS, CGI-S, and the Calgary Depression Scale for Schizophrenia (CDSS) [75] were compared using mixed models for repeated measures and analyses of covariance on the LOCF end point. The lurasidone and ziprasidone groups showed equivalent end point improvements, although with some superiority for lurasidone in the case of the PANSS negative subscale. The same trial also compared the procognitive effects of 3 weeks of treatment with lurasidone 120 mg and ziprasidone 160 mg [74]. Cognitive assessment was based on a large subset of the MATRICS Consensus Cognitive Battery (MCCB) [76] and the Schizophrenia Cognition rating Scale (SCoRS) [77]. Although significant improvements in the baseline MCCB composite score and the SCoRS score were observed in the lurasidone group but not ziprasidone group, no differences emerged in direct comparisons between the 2 treatment groups.

***Short-term open-label study***

The short-term efficacy of lurasidone has been evaluated in a US, multisite, randomized, 6-week, open-label, study of patients with DSM-IV schizophrenia or schizoaffective disorder in a stable, non-acute phase who were switched from their current treatment with antipsychotic medications because of insufficient efficacy and/or safety-tolerability concerns. The results of the trial were subject of 2 publications [78 79]. As reported in detail in the core study [78], after a screening period, individuals were randomized to 1 of 3 open-label arms: lurasidone 40 mg/day for 14 days followed by flexible dosing within the 40–120 mg/day range for the remaining 4 weeks; lurasidone 40 mg/day for 7 days followed by 80 mg/day during the second week and 40–120 mg/day flexible dosing thereafter; and lurasidone 80 mg/day for the first 14 days followed by flexible dosing in the range 40-120 mg/day for the following 4 weeks. The time to treatment failure represented the primary outcome measure. The changes from baseline scores relative to PANSS, CGI-S, and CDSS were used as secondary outcomes and were evaluated in the intent-to-treat population using

analysis of covariance. With the unique exception of the CDSS in the 40 mg group, the switch from previous antipsychotic medication to lurasidone produced a significant reduction of symptom severity in the 3 lurasidone groups, without any appreciable effect of the randomization to one or the other switching procedure. Supplementary dedicated analyses on the effects of switching from previous antipsychotics to lurasidone on health-related quality of life and general health status were the focus of the second publication [79]. A 30-item instrument, the Personal Evaluation of Transitions in Treatment (PETiT) scale [80], and a 12-item scale, the Short Form Health Survey (SF12) scale [81], were administered to 235 patients. At the end point, the PETiT total score improved by 9.1% from the baseline. The improvement involved the domains of the scale relative to adherence-related attitude and psychosocial functioning. Stratification of the sample according to the pre-switch antipsychotic medications showed that the improvement in the PETiT total score at the end point occurred in patients switched from quetiapine, risperidone, aripiprazole, and ziprasidone but not those switched from olanzapine. When the pre-switch antipsychotics were aggregated into sedating and non-sedating groups, it emerged that the improvement in the PETiT total score involved the patients switched from non-sedating antipsychotic medications. In turn, the results relative to the SF-12 scale showed that the switch to lurasidone promoted an improvement in scores relative to the mental components but not the physical components of the scale, with a major effect in patients switched from non-sedating antipsychotics.

## Long-term efficacy

The long-term efficacy of lurasidone in people with schizophrenia has been evaluated in 4 multicentre studies, 2 double-blind and 2 open-label. One double-blind study was originally designed as a long-term trial. The remaining double-blind study and the 2 open-label trial were extension trials.

### *Double-blind studies*

The long-term, double-blind, double-dummy trial that compared lurasidone with risperidone [82] was carried on at 68 sites in North and South America, Asia, Africa, and Europe over a 12-month period, and involved patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder who had an illness duration of at least 1 year, were clinically stable for at least the previous 8 weeks, and had not changed their antipsychotic therapy for at least 6 months before the screening visit. After a transition phase up to 7 days to discontinue antipsychotic medications, the patients were randomized in a 2:1 ratio to lurasidone or risperidone. Lurasidone was administered at 80 mg/day during the first week of treatment and was maintained within the 40–120 mg/day range thereafter. Risperidone was given at 2 mg/day during the first 2 days of treatment and increased to 4 mg/day on day 3, with the possibility of changing the dosage to between 2 and 6 mg/day by day 8. Patients were instructed to take the study medication once daily with the morning meal or within 30 minutes after eating. In the case of sedation, the therapy could be taken with the evening meal. Four hundred nineteen and 202 patients received at least one dose of lurasidone or risperidone, respectively. The trial had the primary objective of monitoring the long-term safety and tolerability of the 2 study medications. The efficacy analysis involved the intent-to-treat population and used a Cox regression survival model and a mixed model for repeated measurements. Twenty percent of the lurasidone patients and 16% of those randomized to risperidone relapsed at some point during the study period. The 1.31 hazard risk (95% confidence interval, 0.87–1.97) proved the lack of differences between the 2 medications. The scores relatives to the total PANSS, the PANSS positive, negative, general psychopathology and cognition subscales, the CGI-S, and the MADRS decreased continuously over the 12-month period; once again no significant difference between the 2 antipsychotics was found.

The double-blind extension study [83] had a 12-month parallel-group, non-inferiority design, compared flexible dose ranges of lurasidone (40-160 mg/day) and quietapine XR (200-800 mg/day), and involved consenting patients who had completed the original 6-week, placebo-controlled, fixed-dose trial [68]. Overall, 151 patients continued taking lurasidone and 85 patients continued taking quetiapine XR. The 56 patients treated with placebo in the 6-week trial were treated with lurasidone. The primary outcome at the end point was a non-inferiority comparison relative to relapse prevention for which a Cox proportional hazards model was used. The changes in total PANSS, PANSS subscales, CGI-S, and NSA-16 were the secondary outcome measures and mixed models for repeated measurements were used. Compared with patients on quetiapine XR those in the lurasidone group showed a 27.2% and 56.7% reduction in the risk for relapses and hospitalizations due to relapse, respectively, over the 12 months. Further-

more, at the 12-month end point, the group that continued with lurasidone showed greater improvement in total PANSS and PANSS positive subscale scores than patients treated with quetiapine XR. These differences persisted independently from the selection, as point of reference, of the baseline score assessed at the beginning of the acute trial or the 12-month extension study. Interestingly, in a post hoc comparison [84] that considered only the patients on quetiapine XR treated with doses higher than 400 mg/day, that is, with doses reported to be associated with improved efficacy [85], lurasidone was not found to be inferior to quetiapine XR for long-term maintenance treatment of schizophrenia. In the core study [83], the improvement in the MADRS score was superior in patients who continued on lurasidone than in those who persisted with quetiapine XR; however, the difference emerged only when the acute baseline score was used. The group of patients who completed the initial 6-week trial with placebo and were included in the supplementary long-term lurasidone arm showed improvements in the various rating scales that were largely comparable with those observed in the group that continued with lurasidone. The first 6 months of the double-blind extension study were also used to evaluate the effects of lurasidone on cognitive performances and functional capacity [70]. At the end of the 6-month period, the group that continued with lurasidone had improved composite Z scores for the CogState computerized cognitive battery in comparison with the quetiapine XR group. Lurasidone and quetiapine treatments were associated with continued improvements in the UPSM-B total score, without evidence of differences between the treatments.

***Open-label extension studies***

The 2 open-label extension studies lasted for 6 months and focused primarily on long-term safety and tolerability.

In one study [86], patients with DSM-IV schizophrenia who completed the 6-week, placebo-controlled trial [62], which also included an olanzapine arm for sensitivity analyses, were given the option to continue with lurasidone for a further 6 months. Irrespective of the original randomization to lurasidone, placebo or olanzapine, the patients who consented to take part in the extension study received a 3-day single-blind, placebo-controlled washout followed by 7 days of therapy with lurasidone 80 mg/day. Thereafter, they were treated with flexible doses of lurasidone within the 40–120 mg/day range. Lurasidone was administered once a day in the morning, with food. Efficacy was the secondary outcome measure and was measured by calculating the changes at the end point from baseline in total PANSS, PANSS positive, negative, and general subscales, and CGI-S. The scores relative to the beginning of the 6-week double-blind trial and the 6-month open-label study were used as the baseline reference values. One hundred thirteen of the 254 patients who took part in the extension study completed the supplementary 28 weeks of treatment. Patients showed continued improvement in total PANSS score, although with some differences according to the original randomization to lurasidone, placebo or olanzapine in the short-term double-blind study [62]. A similar pattern of change was reported, but not explicitly quantified, with regard to the PANSS positive, negative and general subscales, and the CGI-S.

The other multicentre, open-label, 6-month, extension study [87] was a continuation of the 6-week, open-label study [78] in which non-acute, stabilized outpatients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder were switched from other antipsychotic medications to monotherapy with lurasidone. The 149 patients who took part in the extension study started with the same lurasidone dose that they received at the completion of the 6-week trial. Thereafter, flexible adjustments of the lurasidone dose between 40 and 120 mg/day were permitted. Lurasidone was taken on a once-daily basis in the evening, with food or 30 minutes after eating. Although the study was mainly designed to assess the long-term safety and tolerability, the changes in total PANSS, PANSS positive, negative and general subscales, CGI-S, and CDSS were taken into account as secondary end points. Two baseline references were considered: the beginning of the 6-week core study and the beginning of the 28-week extension study. A one-sample t-test of the least squares means was used for the statistical analyses. The extension study was completed by 65.8% of the patients who agreed to participate. When the point of reference was the baseline score relative to the beginning of the initial 6-week trial, the changes in the different rating scales at the end point were significantly reduced. When the baseline values at the beginning of the extension study were considered, no significant improvement was observed at the end point.

## Pooled post hoc analyses of RCTs

The efficacy of lurasidone for the treatment of schizophrenia has also been evaluated in 3 pooled, post hoc analyses of RCTs.

A first pooled analysis [88] involved 4, 6-week, placebo-controlled RCTs and used the 5 PANSS-derived Marder factors [89] derived from the PANSS. The analysis was finalized to assess the possibility of preferential effects of lurasidone on defined domains of psychopathology. Lurasidone was superior to placebo in improving each Marder factor, with effect sizes ranging between 0.31 and 0.43 in relation to the lurasidone dose and the PANSS-derived factor tested over time.

A second pooled, post hoc analysis [90] used the unified database of 4, similarly designed, 6-week, placebo-controlled trials [60 62 63 68] in order to assess the efficacy of lurasidone in the treatment of the depressive symptoms associated with schizophrenia. When the doses of lurasidone were grouped together, the patients randomized to the active medication showed greater reductions in MADRS total score at the end point in comparison with patients on placebo, with a 0.24 effect size. However, some possible dose-related effects emerged; the improvement in the baseline MADRS total score at the end point separated the placebo group from the lurasidone 80 and 160 mg/day arms but not from the 40 and 120 mg/day arms. When the efficacy on depressive symptoms associated with schizophrenia was expressed by the proportion of MADRS responders and remitters, only numerical advantages of lurasidone over placebo emerged, with the unique exception of a higher rate of MADRS remitters on lurasidone for patients in the subsample with a baseline total score of at least 12.

A third pooled, post hoc analysis [91] of the databases of the studies conducted globally evaluated the eventual presence of some effect of race-ethnicity on the efficacy and safety of lurasidone. The non-white/non-black patients presented a numerically larger improvement in PANSS total score but the application of a mixed model for repeated measurement to PANSS and CGI-S data failed to support a treatment by race-ethnicity interaction. Furthermore, no differences in the incidence of treatment-emergent side effects were found in the comparisons between the white, the black, and the non-white/non-black subgroups.

## Safety and tolerability

### *Early discontinuations*

Adverse events (AEs), especially when they are severe, dangerous or stressful, are a common cause of early discontinuation. Therefore, the rate of dropouts ascribable to AEs may be considered a global, reasonable proxy of the safety and tolerability of any medication.

In the 5, 6-week, placebo-controlled RCTs published so far [56 60 62 63 68], the lurasidone-placebo difference relative to the percentage of patients who discontinued the treatment prematurely ranged between -1.9% and 8.2%. These values provide the first, tangible support for the conclusion that lurasidone is a well-tolerated medication for people with schizophrenia.

Also the unique short-term, direct comparison with ziprasidone [73] supports the safety profile of lurasidone; at the 3-week end point, the rate of discontinuation in the group randomized to the medication under investigation (10.4%) was slightly more favourable than the 11.1% found in the ziprasidone arm. Evidence of a substantial equivalence or even a marginal advantage of lurasidone is of some interest because ziprasidone is commonly credited as being one of the safest second-generation antipsychotics [5].

The results from the 4 long-term extension studies [82 83 86 87], substantially support the indication that lurasidone has a good safety profile. The rates of early discontinuation in patients treated with lurasidone ranged between 5.5% and 21.5%. Furthermore, in the double-blind, long-term trial that compared lurasidone with quetiapine XR [83], the percentages of early discontinuations due to AEs were similar (6.6% and 5.4%) in the 2 lurasidone groups and 4.7% in the quetiapine XR group. In the double-blind, long-term comparison with risperidone [82], the percentage of early discontinuations observed in the lurasidone group (21.5%) exceeded the rate (14.4%) found for the risperidone arm.

### *Adverse events*

The incidence of at least 1 AE in patients randomized to lurasidone in placebo-controlled RCTs [56 60 62 63 68] varied from 85.5% to 57.6%, according to the specific trials. The comparisons with the rates observed in the corresponding placebo groups never reached significance. Equivalent figures for patients reporting at least 1 AE were also found in the case of quetiapine XR and olanzapine when these medications were included as active controls for analyses [62 68]. Furthermore, in the 3-week, direct, double-blind comparison with ziprasidone 160 mg [73], at least one AE was reported by 56.7% and 65.5% of the patients randomized to lurasidone 120 mg or to the comparator medication, respectively. In all the short-term RCTs, most of the AEs were rated as mild to moderate, irrespective of the treatment arm considered.

The incidence of severe AEs was systematically below the 10% threshold and the figures relative to lur-

asidone, placebo and, when present, quetiapine XR and olanzapine, were similar. The lack of any treatment difference in the rate of severe AEs was also supported by the 3-week, direct comparison with ziprasidone [73]: 6.7% of patients on lurasidone and 7.3% of individuals randomized to ziprasidone.

In relation to the AEs most commonly associated with taking lurasidone, the evaluation focused on the 5 published, 6-week RCTs and was restricted to the events registered with a at least 5% incidence in a single trial. These RCTs were of similar experimental design and were sufficiently powered for comparisons with placebo. Furthermore, because the RCTs presented a wide variability in the incidence of AEs in patients randomized to placebo, the mean values relative to the different lurasidone groups were refined by subtracting the values relative to the corresponding placebo group [92 93].

Two main types of evidence emerged immediately from the inspection of the data (Tables II and III). The first was that the incidence of individual AEs in the lurasidone groups continued to fluctuate across the trials even after adjustment for the placebo reference value; many of the AEs that occurred with a frequency of 5% or more in one trial did not reach the same threshold in many others and some AEs were variably overrepresented in the placebo or the lurasidone groups according to the specific RCT considered. The second was that, when present, the AEs in the lurasidone groups generally involved only a minority of the sample, with akathisia as the major exception to this general trend. Only akathisia and somnolence seemed to be dose related.

Overall, the data relative to the incidence and severity of AEs in the short-term trial strongly support the conclusion that the lurasidone safety profile mimics

**Table II.** Emergent psychiatric and neurologic adverse events*: refined**, comparative incidence between the lurasidone and placebo groups.

| Adverse event | LURASIDONE – PLACEBO Δ difference (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Lur 40 mg | | | Lur 80 mg | | | Lur 120 mg | | | Lur 160 mg |
| | Ogasa et al 2013[68] | Meltzer et al 2011[62] | Nasrallah et al 2013[81] | Nakamura et al 2009[80] | Nasrallah et al 2013[81] | Loebel et al 2013[88] | Ogasa et al 2013[68] | Meltzer et al 2011[62] | Nasrallah et al 2013[81] | Loebel et al 2013[88] |
| Headache | 6 | 0.2 | 2.8 | 1.1 | -2.5 | -1.1 | -3.9 | -3.8 | 1.2 | 1.8 |
| Insomnia | 6 | 1.8 | -0.5 | 6.7 | 0.4 | 2.1 | 8.2 | 0.7 | -3.1 | -2.5 |
| Somnolence | 4 | 5.8 | 5 | 7.8 | 4.4 | 3.2 | 6.2 | 11.2 | 9 | 5.8 |
| Sedation | 8 | 5.8 | 0.9 | 6.6 | 6 | ● | 4.3 | 10.2 | 5.8 | ● |
| Agitation | ● | 6.6 | 4 | ● | 0.9 | -5.1 | ● | 0.7 | 4 | -3.3 |
| Anxiety | ● | 3.2 | ● | 5.6 | ● | -1.1 | ● | 3.3 | ● | -5 |
| Psychotic disorder | ● | -5.2 | ● | ● | ● | -5.8 | ● | 3.5 | ● | -5.8 |
| Dystonia | ● | 2.5 | 4 | ● | 6.6 | ● | ● | 6.7 | 1.6 | ● |
| Restlessness | ● | 3.3 | ● | ● | ● | ● | ● | 0.8 | ● | ● |
| Akathisia | 8 | 10.9 | 8.3 | 5.6 | 14.3 | 7.2 | 14.3 | 2.2 | 21.3 | 6.6 |
| Tremor | 6 | -2.6 | ● | ● | ● | ● | 8.2 | 3.3 | ● | ● |
| Parkinsonism | ● | 7.5 | 6.5 | ● | 4.1 | ● | ● | 9.3 | 9.7 | ● |
| Extrapyramidal disorder | 4 | ● | ● | ● | ● | ● | 6.1 | ● | ● | ● |

*Green: numerically lower incidence in the lurasidone group; Red: numerically higher incidence in the lurasidone group; yellow: equal incidence between the lurasidone and placebo groups; blue: adverse event not included among those with at least 5% incidence in the lurasidone or placebo arm; Lur: lurasidone.*

** Adverse events reported in ≥ 5% of patients during the 6 weeks of treatment with lurasidone or placebo. ** Net percentage in the lurasidone group after subtraction of the corresponding placebo group.*

**Table III.** Emergent medical adverse events*: refined**, comparative incidence between the lurasidone and placebo groups.

| Adverse event | LURASIDONE - PLACEBO Δ difference (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Lur 40 mg | | | Lur 80 mg | | | Lur 120mg | | | Lur 160mg |
| | Ogasa et al 2013[68] | Meltzer et al 2011[82] | Nasrallah et al 2013[83] | Nakamura et al 2009[80] | Nasrallah et al 2013[83] | Loebel et al 2013[88] | Ogasa et al 2013[68] | Meltzer et al 2011[82] | Nasrallah et al 2013[83] | Loebel et al 2013[88] |
| Nausea | 6 | 6.6 | 4.2 | 13.4 | -0.5 | 4.7 | 18.4 | 3.3 | 5 | 3.3 |
| Dyspepsia | -4 | 1.6 | 0.1 | 7.8 | 1.1 | -0.9 | -3.9 | 1.6 | 5 | 2.5 |
| Vomiting | 2 | -2.7 | 0.1 | 5.5 | 1.9 | 1.4 | 2.2 | 1.6 | 5.8 | 2.4 |
| Tooth ache | ● | -1.8 | ● | 2.3 | ● | ● | ● | -2.7 | ● | ● |
| Dry mouth | ● | -0.8 | ● | ● | ● | 0.8 | ● | -1.6 | ● | 0.9 |
| Salivary hypersecretion | ● | 1.7 | ● | ● | ● | ● | ● | 6.8 | ● | ● |
| Appetite decrease | ● | 3.3 | ● | ● | ● | ● | ● | -0.9 | ● | ● |
| Appetite increase | ● | -2.8 | ● | ● | ● | ● | ● | 0.9 | ● | ● |
| Weight gain | ● | -3.5 | 2.4 | ● | 0.9 | 0 | ● | -3.5 | 7.3 | 0.9 |
| Diarrhea | -2 | ● | ● | ● | ● | ● | -8 | ● | ● | ● |
| Constipation | 2 | -0.2 | ● | 5.5 | ● | ● | -6 | 2.4 | ● | -1.7 |
| Arthralgia | ● | ● | ● | ● | ● | 0.8 | ● | ● | ● | 0 |
| Dizziness | 6 | 2.5 | ● | ● | ● | 3.1 | 4.2 | 3.4 | ● | 4.1 |
| Musculoskeletal stiffness | ● | 0.8 | -3.1 | ● | 1.1 | ● | ● | 3.4 | -1.5 | ● |
| Muscle cramp | 2 | ● | ● | ● | ● | ● | 6.1 | ● | ● | ● |
| Back pain | 2 | 0.7 | 0.8 | -2.3 | 4.2 | ● | 4.1 | 0.8 | 0 | ● |
| Pain in limbs | 4 | ● | ● | ● | ● | ● | 0 | ● | ● | ● |
| Fatigue | 0 | ● | ● | ● | ● | ● | -6 | ● | ● | ● |
| Upper respiratory trait infection | ● | ● | ● | -3.4 | ● | 0.8 | ● | ● | ● | 0 |

*Green: numerically lower incidence in the lurasidone group; red: numerically higher incidence in the lurasidone group; yellow: equal incidence between the lurasidone and the placebo groups; blue: adverse event not included among those with at least 5% incidence in the lurasidone or placebo arm; Lur: lurasidone.*

** Adverse events reported in ≥ 5% of patients during the 6 weeks of treatment with lurasidone or placebo. ** Net percentage in the lurasidone group after subtraction of the corresponding placebo group.*

that of placebo and other well-reputed second-generation antipsychotics. This conclusion is largely confirmed by long-term trials [82 83 86 87].

The benign safety and tolerability profile of lurasidone is further reinforced by the short- and long-term trials that explicitly included physical examination, vital signs, electrocardiographic modifications, body weight, metabolic tests, prolactin levels, haematology, blood chemistry, and extrapyramidal symptoms. In particular, lurasidone was not associated with clinically significant treatment-emergent changes relative to body temperature, systolic and diastolic blood pressure, and pulse rate, with the exception of a few sporadic cases of orthostatic hypotension or orthostatic tachycardia. When investigated [60], fundoscopy did not reveal appreciable changes during the treatment with lurasidone. Similarly, lurasidone was substantially devoid of any unfavourable effects on electrocardiographic parameters and had only marginal effects on the Fredericia-corrected QT interval.

There is consistent evidence that lurasidone has minimal effects on body weight, body mass index, and waist circumference. The observation [73] that, over a 3-week period, patients on lurasidone showed a 0.65 kg reduction in median weight supports this conclusion; the group randomized to one of the antipsychotics with the lowest effects on weight gain, ziprasidone, presented a reduction of 0.35 kg. The evidence from short-term placebo-controlled trials is that patients on lurasidone presented changes in these parameters from baseline values that were repeatedly similar to those found in patients on placebo. The rate of patients on lurasidone who developed at least a 7% increase in their baseline body weight was less than the corresponding figure relative to individuals randomized to olanzapine [62], quetiapine

XR [83], ziprasidone [73], and risperidone [82]. The benign influence of lurasidone on body weight was further confirmed in long-term studies. Furthermore, in the extension study [87] relative to a 6-month follow-up of patients switched to lurasidone from previous treatments with second-generation antipsychotics, the proportion of patients switched to lurasidone from olanzapine, quetiapine, risperidone and ziprasidone, with a 7% or more weight loss at the end point exceeded the percentage with a 7% or more weight gain. The body weight changes in patients switched to lurasidone from aripiprazole, i.e. one of the second-generation antipsychotics with the lowest weight gain potential, were less striking [3 4 13].

The data relative to changes in the levels of total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, glucose, $HbA_{1c}$, HOMA-IR, insulin and C-reactive protein coherently indicate that the effect of lurasidone on metabolic parameters and measures of glycemic control are minimal and similar to those found in patients on placebo. In addition, direct and indirect comparisons with other second-generation antipsychotics strongly suggest that lurasidone should be considered to be decidedly preferable to olanzapine [86], much better than risperidone [82], and at least equivalent to quetiapine XR and ziprasidone [73 83] with regard to metabolic and glycemic safety. Similarly, clinical trials have substantially failed to demonstrate clinically significant treatment-emergent modifications in haematology and blood chemistry.

Regarding the influence of lurasidone on plasma prolactin levels, it seems sufficiently proven that hyperprolactinaemia-related events such as galactorrhoea, sexual dysfunction, and disturbances of the menstrual cycle are uncommon. Furthermore, the increase in prolactin induced by lurasidone was generally modest, frequently equivalent to the fluctuations observed in patients randomized to placebo, and subject to a gender effect, with greater increases in females than in males. Data derived from the RCTs that included an active comparator also suggest that the magnitude of the effect of lurasidone on prolactin levels is inferior to that induced by olanzapine [62] and risperidone [82] and equivalent or marginally superior to that observed in patients treated with ziprasidone [73] or quetiapine XR [68 83]. However, the short-term data relative to olanzapine and quetiapine XR are not supported by statistics because the 2 antipsychotics were included exclusively for sensitivity analyses.

Despite akathisia and parkinsonism being at the top in the list of the most frequent AEs with lurasidone, the short- and long-term trials supported a fairly benign profile of this medication in relation to the signs and symptoms assessed by the Simpson-Angus Scale (SAS) [94], the Barnes Akathisia Scale (BAS) [95], and the Abnormal Involuntary Movement Scale (AIMS) [96]. In lurasidone-placebo comparisons of the changes from baseline SAS and AIMS scores at the end point, the second-generation antipsychotic was frequently comparable with placebo [56 60 62 63 68]. With regard to changes in the baseline BAS score at the end point, a modest advantage of placebo sometimes emerged. Placebo-controlled trials also suggested the existence of a possible dose-response effect. The changes from SAS, BAS and AIMS baseline scores observed in patients on lurasidone were also similar to those observed in patients treated with ziprasidone [73] and quetiapine XR [68]. A substantial equivalence with olanzapine was found in the lurasidone 40 mg arm [62]. Furthermore, in a 12-month direct trial [82], patients on lurasidone but not risperidone showed a small but significant increase in BAS total score compared with placebo at the LOCF end point. The demonstration [78] that more than the 90% of the patients switched to lurasidone from another second-generation antipsychotic medication presented, after 6 weeks of treatment with lurasidone, unchanged or improved SAS, BAS and AIMS scores suggests that lurasidone has an effect on extrapyramidal signs and symptoms that is equivalent or even better to that of other second-generation antipsychotics. The long-term trials [82 83 86 87] indicated that the short-term, marginal effects of lurasidone on SAS, BAS and AIMS induced early by lurasidone persist without meaningful modifications when the treatment is prolonged over time.

### *Relationship between daytime sleepiness, agitation, cognition and functional capacity*

As reported earlier, somnolence and sedation are among the solicited and spontaneously reported AEs most commonly found in people treated with lurasidone. Nevertheless, direct evidence emerging from clinical trials and multiple-treatment meta-analyses [5] have clearly indicated that lurasidone is characterized by a relatively benign potential to induce somnolence or sedation. Furthermore, unlike most of the remaining antipsychotic medications, lurasidone has been explicitly investigated for its effect on daytime sleepiness [97] using the Epworth Sleepiness Scale (ESS), a patient-reported, 8-item questionnaire [98]. In an ancillary publication of a previously published, international, 6-week, double-dummy RCT that compared lurasidone 80 and 160 mg/day with placebo and quetiapine XR 600 mg/day [68], the ESS total

score at the end point was reduced from baseline in the lurasidone and placebo groups but increased in the quetiapine XR arm. The same report also challenged the influence of daytime sedation on agitation, cognitive performance and functional capacity using the PANSS excitement subscale (PANSS-EC) score [99], the CogState composite Z score, and the UPSA-B total score. Agitation improved in patients on quetiapine XR, lurasidone 80 mg and lurasidone 160 mg more than in patients on placebo, and sedation was found to be associated with a reduction of agitation in the quetiapine XR group but not in the 2 lurasidone arms. Furthermore, the cognitive performance of patients on lurasidone 160 mg at the end point was superior to that of the patients randomized to placebo or quetiapine XR, and the quetiapine XR but not the lurasidone and placebo groups showed an association between worsening of cognitive performance and an increase in the score for the ESS item "dozing when talking to someone". Increased levels of sedation expressed by a higher ESS total score was also associated with a worsening of functional capacity expressed by the UPSA-B total score.

## Economic impact

So far, no study has directly estimated the health care costs of lurasidone in the treatment of people with schizophrenia treated in typical clinical settings. Two studies [100-101] have used economic models.

The first study [100] compared the cost-effectiveness over 5 years of lurasidone and aripiprazole in the treatment of patients with schizophrenia who had previously failed at least a trial with another second-generation antipsychotic. The rate of total discontinuations, relapses, and hospitalizations were modelled in a Markov cohort analysis together with inputs of the costs due to pharmacy, mental health, and cardiometabolic risk. In the model, the characteristics of the patients reflected the average person with schizophrenia enrolled in lurasidone trials and the effectiveness inputs were derived from multi-step, indirect comparisons of lurasidone and aripiprazole using other antipsychotics included in the CATIE phase 1 study as intermediaries [24]. The model indicated a saving of $4019 with lurasidone over the 5-year period (Fig. 2) despite the higher pharmacy costs of lurasidone in comparison with aripiprazole.

The second study [101] estimated the potential economic impact of annual relapses and relapse-related hospitalizations in patients with chronic schizophrenia treated with lurasidone or quetiapine XR. A dedicated economic model was developed in which the costs relative to the use of inpatient and outpatient mental health care-related services as they emerged in a prospective, observational usual-care study in the United States [102] were applied to the rates of relapses and relapse-related hospitalizations that occurred during a short-term RCT and its double-blind, 12-month extension trial [68 83]. Probabilistic analysis estimated that lurasidone produced a per-patient per-year saving of $3276 and $2702 (Fig. 3) when the total mental health care-related costs were referred to the relapse-related hospitalizations or the relapses in general, respectively.

## Comments

The current literature on the efficacy and tolerability of lurasidone offers 3 key evidence-based factors for concluding that this second-generation antipsychotic should be included among the first-line options at the disposal of clinicians for the treatment of people with schizophrenia.

The published placebo-controlled trials [56 60 62 63 68] systematically indicate that lurasidone combines fast, valuable antipsychotic efficacy together with unusually wide margins of safety and tolerability when given to patients with an acute exacerbation of schizophrenia. Short-term trials [73 78] also provide some initial evidence that lurasidone is indicated for patients with schizophrenia who manifest a stable, non-acute phase of the disorder.

Long-term studies [82 83 86 87] demonstrate that the favourable efficacy and safety profile of lurasidone is maintained over time.

The few short- and long-term trials with an active comparator [73 82 83] underline that, compared with other second-generation antipsychotics, lurasidone combines a substantially equivalent efficacy with a moderately to appreciably superior tolerability. The comparisons [62 68] of placebo with olanzapine or quetiapine XR in trials that included a group treated with an active control for sensitivity analysis purposes add further, indirect support for this last conclusion.

Thus, the approvals of the international agencies for the use of oral lurasidone in the short- and long-term treatment of schizophrenia appears strongly supported, given that that all the RCTs satisfy the criteria [103] for a high-quality score.

These general comments on the effects of lurasidone in people with schizophrenia can be enriched with a number of supplementary, more specific considerations.

Lurasidone plausibly shows a broad spectrum of an-

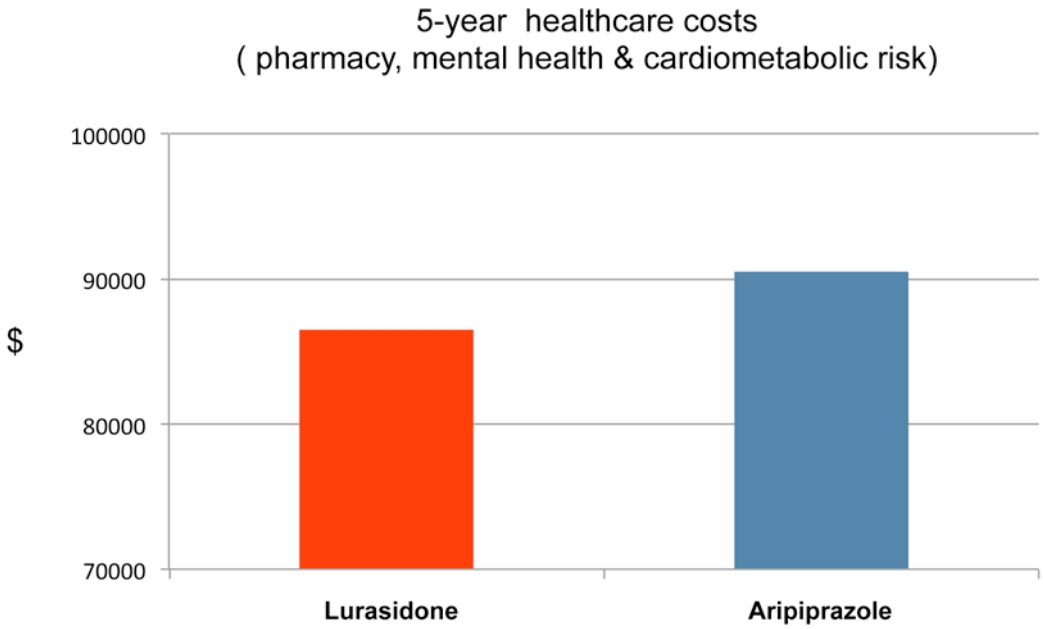


FIGURE 3.
Cost-effectiveness of lurasidone and aripiprazole in patients with schizophrenia who failed at least one trial with another second-generation antipsychotic: results from a Markov cohort model (values reported in Rajagopalan et al. [100]).

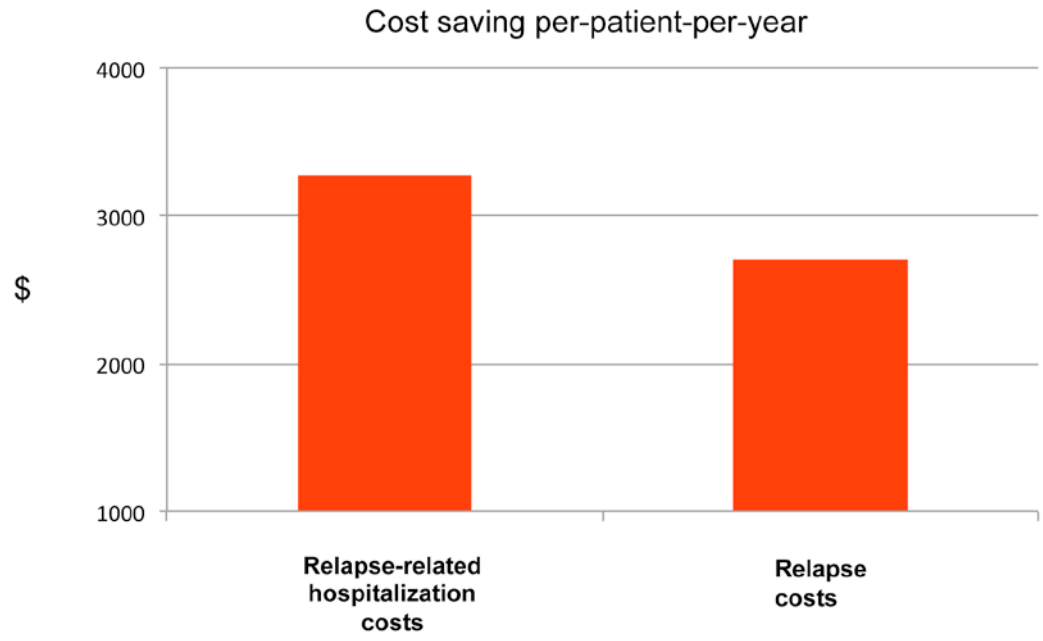


FIGURE 4.
Annual saving with lurasidone in mental health care cost relative to relapses or relapse-related hospitalization: results from a probabilistic model (values reported in Rajagopalan et al. [101]).

tipsychotic activity and may therefore be prescribed for patients with schizophrenia irrespective of the specific symptom pattern presented. Almost all the trials and pooled analyses that tested the PANSS subtypes and the various PANSS-derived factors failed to demonstrate any appreciable indication for symptom-selective efficacy. Therefore, for acute or partially stabilized patients, clinicians should carefully consider the lurasidone option whenever they are starting or switching an antipsychotic medication. However, evidence of efficacy covering the multiple psychopathologic domains of schizophrenia does not exclude that, compared with other antipsychotics, lurasidone could have a greater or lesser efficacy on

defined symptom patterns or that its efficacy could be predicted by defined symptom domains.

The weight of evidence supporting the efficacy of lurasidone for the treatment of depressive symptoms of patients with schizophrenia appears promising. In the long term [83], lurasidone displayed some superiority in comparison with quetiapine XR, the first antipsychotic medication to have received a formal indication for the treatment of resistant major depression. In a pooled analysis [90], the effect sizes computed for the different doses of lurasidone were of clinical interest because they ranged between 0.25 and 0.34. The antidepressant properties of lurasidone in schizophrenia are also supported by other preclinical and clinical findings. In animals, lurasidone has been demonstrated to have antidepressant-like activity [37 42 90 104 105]. Furthermore, 2 randomized, double-blind, placebo-controlled pivotal trials [106 107] have demonstrated an efficacy of lurasidone in bipolar depression, enough to justify approval by the US Food and Drug Administration and Health Canada for the use of lurasidone, either alone or in adjunction with lithium or valproate, for the treatment of major depressive episodes associated with the bipolar I disorder. Similar to other medications that have genuine antidepressant activities, the antidepressant effect of lurasidone was magnified by the presence, at baseline, of severe depressive symptoms [60 90].

The level of evidence on the beneficial properties of lurasidone on neurocognition is decidedly weaker in comparison with the evidence that supports its antidepressant effect. Independently from the rough results of the RCTs that indicate improvements in the cognitive domain of the PANSS, the current body of evidence is restricted to a short-term comparison with ziprasidone [74] and a short- and long-term comparison with quetiapine XR [70]. The duration of direct, double-blind comparison with ziprasidone, 3 weeks only, could be considered not long enough to assess the procognitive activities of a medication. Despite these obvious limitations, the current body of evidence appears promising. Lurasidone was not only associated, unlike ziprasidone, with small but significant improvements in MCCB and SCoRS ratings even after 3 weeks of treatment [74] but was also better than quetiapine XR in improving the neurocognitive composite Z score at the end of both the 6-week acute RCT and the 6-month extension study [70]. Furthermore, the comparisons with an active control produced effect sizes that were encouraging: 0.43 in comparison with ziprasidone relative to the 3-week change in the SCoRS total score [74] and 0.57 in the comparison with quetiapine XR relative to the 32-week change in the composite Z score [70]. A genuine procognitive effect of lurasidone is also supported by the demonstration that the advantage of lurasidone in comparison with quetiapine XR at week 32 persisted after controlling for the changes over time in total PANSS and the positive and negative PANSS subscales [70]. These results are even more favourable considering that neurocognition was assessed using independent, well-validated instruments. Furthermore, referral to composite Z scores in the comparison with quetiapine XR [70] and systematic evaluation [70 74] of multiple aspects of neurocognition gives some practical meaning to the results; significance in tests relative to a single aspect of cognition may be relevant for a better understanding of the pathophysiology of schizophrenia but may have scarce clinical impact. Evidence from preclinical studies [37 38 45], in particular those relative to animal models of cognition and activity on 5-$HT_7$ and 5$HT_{1A}$ receptors, are in agreement with the hypothesis that lurasidone exerts a potential procognitive action.

The demonstration, although in only 1 RCT [97], that lurasidone and quetiapine XR differ not only in the potential to induce sleepiness but also in the levels of mediation exerted by sedation on the outcomes of agitation, cognition, and functional capacity was not completely unexpected. Some medication-specific characteristics at the level of receptor pharmacology [42 97 108 109], especially those relative to affinity at $H_1$ and 5-$HT_7$ receptors, could justify the distinctive clinical effects of the 2 medications on sleepiness and associated phenomena. Irrespective of these considerations, the effects of lurasidone on sedation, agitation, cognition, and functional capacity show promise to add appreciable value of this medication in the therapy of schizophrenia. An antipsychotic medication that reduces agitation without inducing sleepiness and without relevant negative effects on cognitive performance and functional capacity is candidate to become a reasonable first-choice treatment option whenever psychomotor agitation and preservation of functioning are priority targets of the treatment. Considering the well-documented, negative interference of daytime somnolence and sedation on concentration, alertness and daily work performance, and the increased risk for both workplace and car crash injuries [97], the indication for control of agitated behaviour without sedation does not constitute a mere niche in the therapy for people with an acute exacerbation of schizophrenia.

The demonstration [91] of a lack of substantial differences in the efficacy and tolerability profiles of lurasidone between patients stratified according to race suggests that, from a merely clinic perspective, the influence of

ethnicity on the pharmacodynamics and pharmacokinetics of this medication can be plausibly classified as weak. This conclusion is far from being trivial considering the widespread commercialization of lurasidone and the growing, worldwide trend of psychiatric services faced with multi-ethnic populations. However, it must be taken into account that the current evidence derives only from a pooled analysis and that the tripartition of the patients into whites, blacks, and non-whites/non-blacks is decidedly rough.

The body of evidence on the safety and tolerability of lurasidone is rich enough to conclude that it deserves to be considered to be at least competitive or, in some aspects, even better than many antipsychotics on the market. This conclusion is further strengthened by the persistence, even after correction for placebo, of a remarkable variability between the studies in the incidence of AEs that occurred during treatment with lurasidone; discrepant patterns of AEs among the trials make it plausible that some of the associations with lurasidone may be mere chance findings or related to the presence of confounding effects by so far uncontrolled sources of variation. The possible superiority of lurasidone is especially evident with regard to metabolic and cardiovascular risks. The indication to place lurasidone among the preferential therapeutic options for patients with schizophrenia and medical comorbidities or physical AEs associated with the use of other antipsychotics is therefore supported.

National health care services and third-party payers in general identify detailed pharmacoeconomic evaluations as a priority area of interest with obvious strategic significance in this period of worldwide economic restrictions. Nevertheless, current knowledge on the impact of lurasidone on the health care costs of schizophrenia invites some optimism but cannot be considered conclusive because it originates from only 2 studies [100 101] that applied probabilistic models to estimate the direct costs associated with the treatment of patients with schizophrenia. The data related to quality of life and general health status are equally promising but must be considered as preliminary [79].

Most studies on lurasidone in schizophrenia adopted an RCT design. Therefore, current knowledge on the use of lurasidone in schizophrenia is not completely generalizable to the entire population affected by the disorder; patients with problematic informed consent, compulsory treatment, suicidal risk, aggressiveness, and relevant psychiatric or medical comorbidities are generally excluded in RCTs.

Current knowledge on the long-term use of lurasidone is based on one original trial [82] and 3 extension studies [82 83 86 87]. Consequently, the results refer to a special, enriched population of patients who, in acute conditions, responded to the treatment without developing unacceptable AEs. Whether a maintenance therapy with lurasidone is also indicated for patients with schizophrenia who responded poorly to lurasidone during an acute phase of the disorder remains untested. Therefore, no inferences are possible on the degree of continuity or discontinuity that exists between the mechanisms of action of lurasidone in the therapy of the different phases of schizophrenia. From a merely clinical perspective, the impact of this unresolved issue seems marginal. In daily practice, physicians typically maintain the patients on the same medications used with success in acute psychotic breakdowns. Furthermore, the extension study design is the standard of reference for trials on the long-term treatment of patients with schizophrenia, irrespective of the medication time tested. Therefore, the lack of generalizability of the results is an inherent limitation that is not specific to lurasidone.

All lurasidone trials carried out so far are at risk of industry-sponsored bias [110-116] because they have been systematically supported by the manufacturer of the medication. However, the randomized design, the prevalent selection of placebo as the reference comparator, the recruitment of sufficiently powered sample sizes, the use of appropriate statistical methods, the systematic use of internationally accepted outcome measures, the detailed descriptions of the causes of early discontinuations, the publication in peer-reviewed, quality international journals, and the appreciable quality score [103] that can be attributed to the trials protect against eventual industry-sponsored biases.

## Conclusions

The scientific literature strongly supports the conclusion that clinicians can now be confident in prescribing lurasidone for their patients affected by schizophrenia. The scientific literature, however, also supports with vigour the need for further clinical research. The issues relative to the impact of lurasidone on quality of life, health status, and health care costs are among the hot topics that have been so far only been touched on. The same statement applies to the areas of the efficacy of lurasidone on depressive symptoms and cognitive deficits associated with schizophrenia. High priority should also be given to some persistently ignored but clinically relevant issues such as the usefulness of lurasidone in the treatment of patients with aggressive behaviour, uncooperativeness, suicidal risk, and comorbid

substance-related disorders. Individuals at the first episode of schizophrenia, adolescents, and elderly people should be also explicitly studied.

Another new area of investigation for the promotion of awareness of lurasidone should involve medication adherence. Current knowledge is limited to an encouraging but indirect and unreplicated extrapolation related to changes in the PETiT domain of adherence-related attitude [79]. In addition, referral to the global profile of lurasidone appears poorly informative from the perspective of medication adherence. Some of the main characteristics of lurasidone suggest opposite effects: the once-a-day administration and the excellent tolerability profile should have a positive influence, whereas the lack, unlike most of the principal competitors, of a long-acting injectable formulation could be a limiting factor in prescribing lurasidone for patients with schizophrenia at risk for poor medication adherence. Considering that medication adherence constitutes an unsurmountable limiting step with any successful pharmacotherapy [117], long-term comparative studies between lurasidone and other antipsychotics providing the long-acting option are therefore highly indicated.

With regard to residual doubts on industry-sponsored biases, any possibility of a deep understanding obviously requires independent decisions by the manufacturers of medications with the same clinical indication.

Moving from the research areas worthy of prompt implementation to the experimental designs that should be applied to lurasidone studies, RCTs, especially those based on direct comparisons with other antipsychotics, are clearly the indisputable benchmarks for evidence-based use of lurasidone. However, it is also evident that RCTs alone are unlikely to have enough driving force to govern clinical routine. The results of the RCTs are hardly generalizable due to the narrow selection criteria. Furthermore, the RCT design may be far from the optimum when some particular research objectives are to be pursued, for example, when the study focuses on health care costs, the identification of markers of efficacy and tolerability, or the treatment of special populations that are generally excluded from this type of trial. Therefore, RCTs on lurasidone should be partnered with large-scale, real-world, naturalistic or quasi-naturalistic studies representative of the everyday complexities typically found in daily clinical practice. A pragmatic combination of these 2 experimental approaches is crucial for promoting correct prescription patterns and, consequently, the competitiveness of a new medication on the market.

***Conflict of interest***

In the last 3 years, Professor Sacchetti has received funding for consultancy, research, advisory board membership, and sponsored lectures from Angelini, Chiesi, Edra LSWR, Eli Lilly, Janssen-Cilag, Lundbeck, McCann, Otsuka, Pfizer, Roche, Rottapharm, Servier, Stroder, Takeda and Valeas. He has also received grants from the Italian Ministry of Research and the University and Health Authority of Lombardy Region. Professor Sacchetti is an editorial consultant for Edra LSWR and editor in chief of Evidence-based Psychiatric Care. He is not a shareholder in any pharmaceutical company.

In the last 3 years, Professor Vita has received funding for consultancy, research, advisory board membership, copyright and sponsored lectures from Astra Zeneca, Chiesi, Eli Lilly, Forum Pharmaceuticals, Janssen-Cilag, Lundbeck, Otsuka, Roche, Springer. He has also received grants from the Italian Ministry of Research and University and from the Health Authority of Lombardy Region. He is not a shareholder in any pharmaceutical company.

## Take home messages

- Lurasidone is a second-generation antipsychotic that has received approval from many regulatory agencies for the treatment of people with schizophrenia
- Lurasidone has a recommended dose between 40 and 160 mg/day
- Lurasidone needs once-daily dosing after meals of at least 350 kilocalories
- Lurasidone has demonstrated short-term efficacy in both acute and stabilized patients with schizophrenia
- Lurasidone maintains efficacy even in the long term
- Lurasidone may have antidepressant and procognitive effects but any conclusion should be postponed because of insufficient evidence
- Lurasidone is generally well tolerated thanks to a very benign global tolerability profile and almost neutral effect on cardiometabolic activity

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