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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

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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-

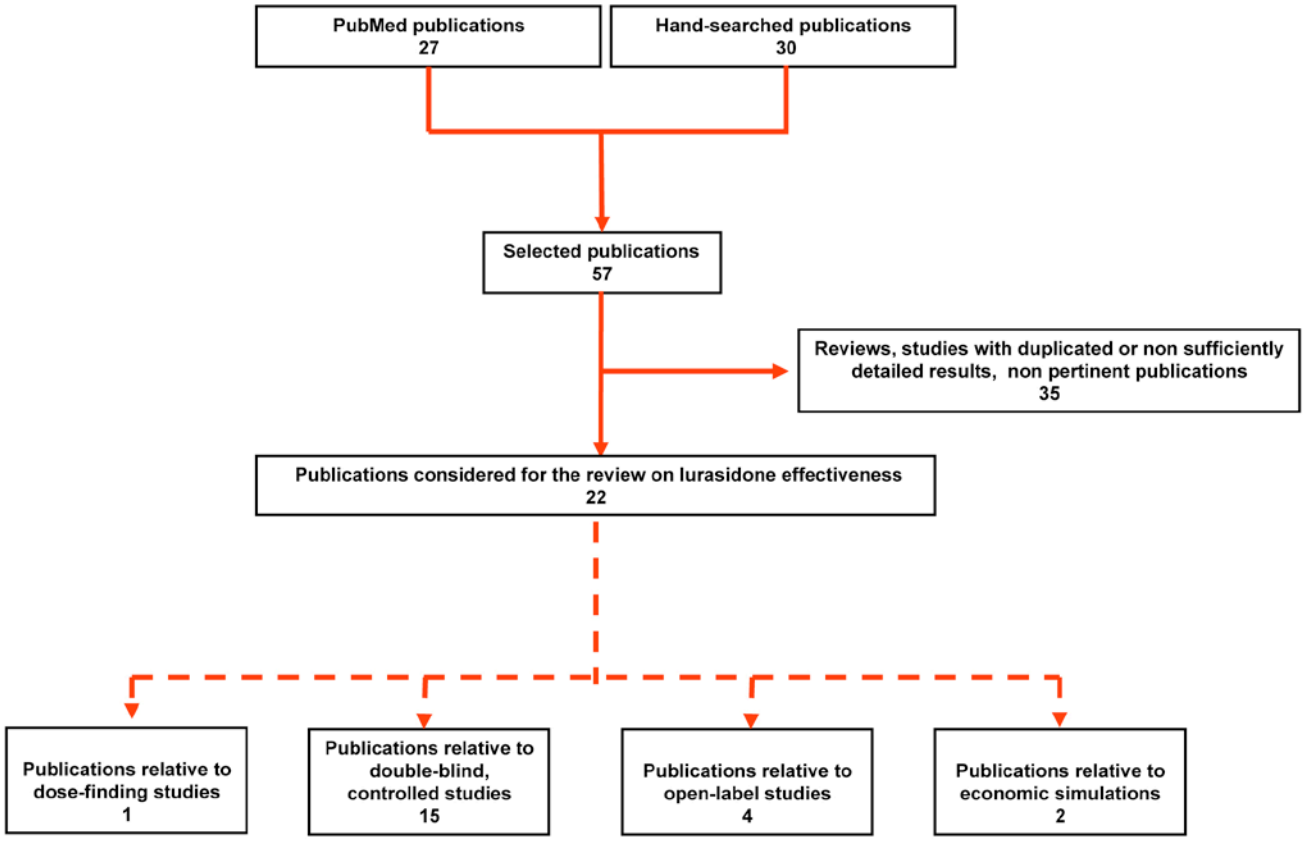

FIGURE 1.

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-

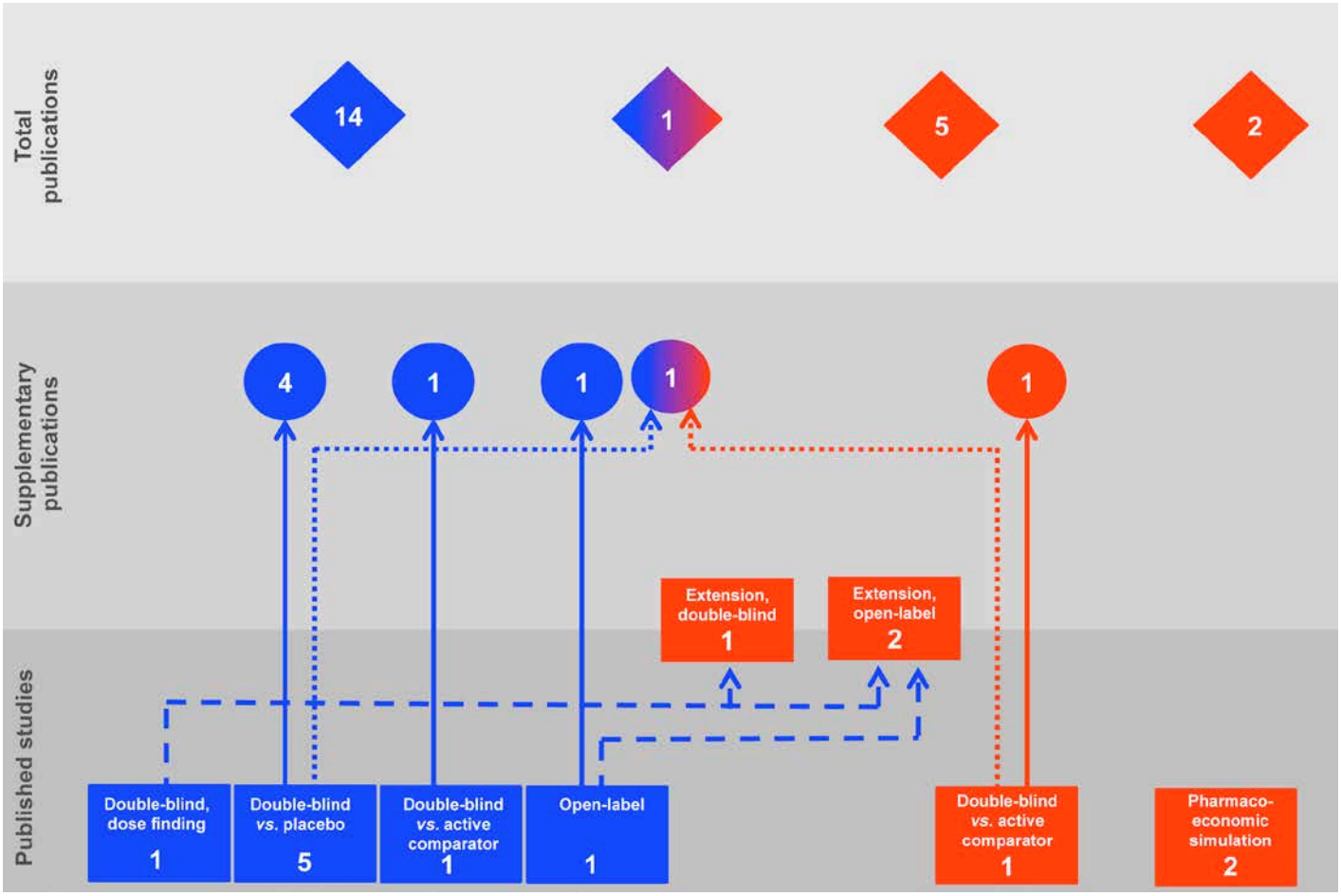

FIGURE 2.

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-

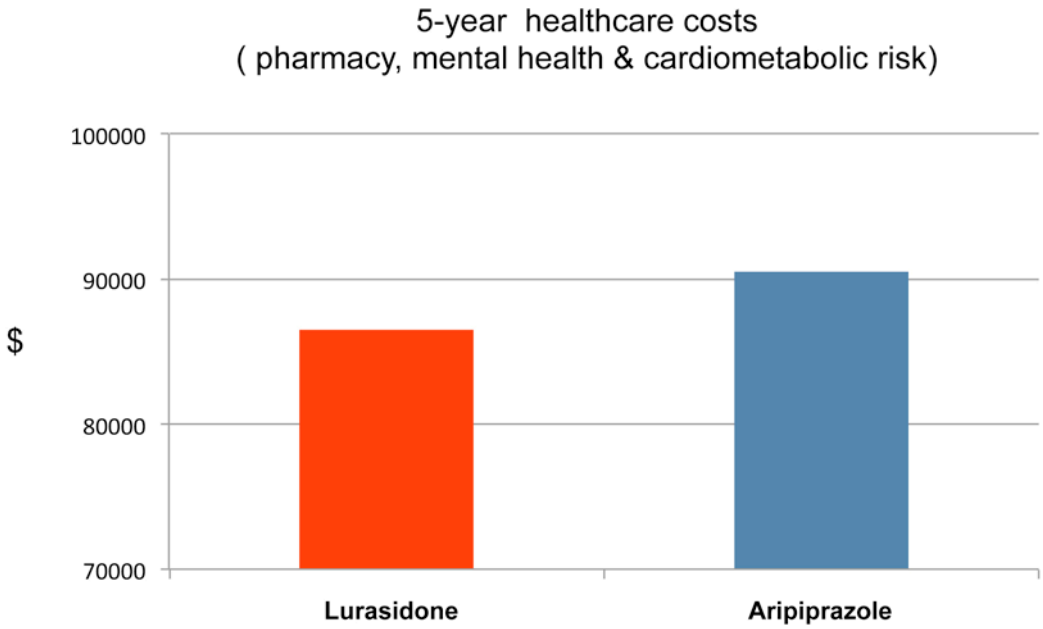

FIGURE 3.
Cost-effectiveness of lurasidone and aripiprazole in patients with schizophrenia who failed at least one trial with another second-generation antipsychotic: results from a Markov cohort model (values reported in Rajagopalan et al. [100]).

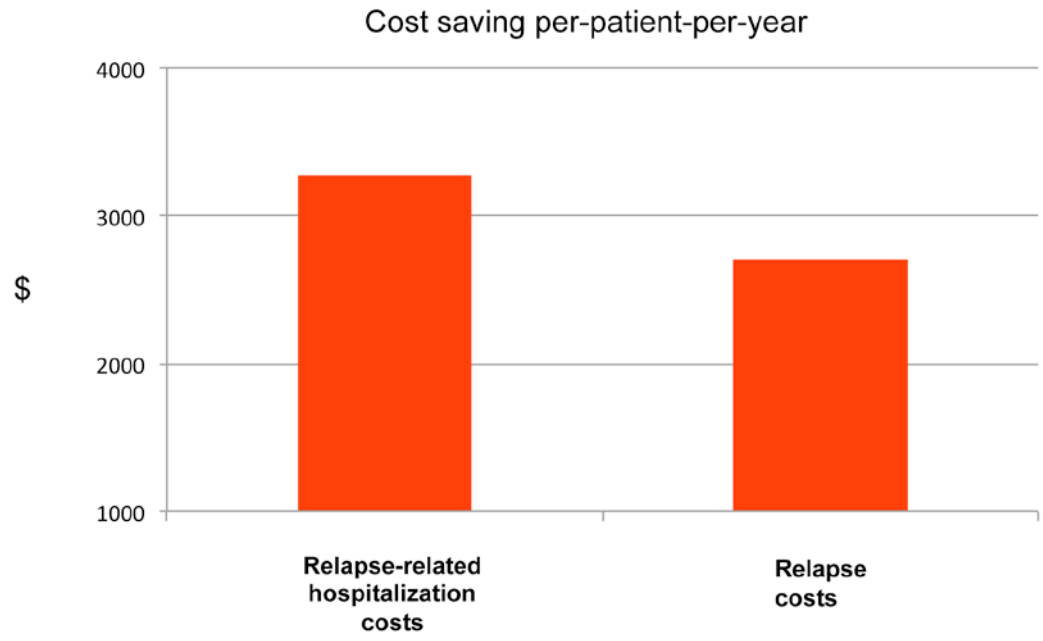

FIGURE 4.
Annual saving with lurasidone in mental health care cost relative to relapses or relapse-related hospitalization: results from a probabilistic model (values reported in Rajagopalan et al. [101]).

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 5HT_{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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