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Impact on carer burden when stable patients with schizophrenia transitioned from 1-monthly to 3-monthly paliperidone palmitate

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ABSTRACT

Rationale: Reducing the frequency of long-acting injectable antipsychotic medication may reduce carer burden.
Objectives: To evaluate the impact of reduced frequency of long-acting injectable antipsychotic medication on carer burden in stable patients with schizophrenia.
Methods: Carer burden was assessed using the Involvement Evaluation Questionnaire (IEQ) within a 52-week, prospective, single-arm, non-randomised, open-label, international, multicentre study evaluating the impact of transitioning stable patients with schizophrenia to paliperidone palmitate 3-monthly (PP3M) from paliperidone palmitate 1-monthly (PP1M).
Results: 159 carers completed the IEQ (mean [standard deviation, SD] age: 54.8 [12.8] years); 52.2% were the patients' parent and > 50% had >32 h/week of patient contact. At baseline, mean [SD] IEQ total score was in the lower range (23.8 [12.6]), reflecting patient stabilisation. At last observation carried forward (LOCF) endpoint, the IEQ total score decreased by a mean (95% CI) of −4.0 (−5.9, −2.1), indicating a significant overall reduction in carer burden ($P < 0.0001$). The six IEQ items with the highest carer burden at baseline were within the urging and worrying domains, in which burden was significantly improved at LOCF endpoint ($P < 0.0001$). Exploratory analyses found that higher carer burden was associated with lower functional remission (Personal and Social Performance score >70) at baseline and LOCF endpoint, and with the patient being part of the carer's household. Shorter disease duration correlated with better general health of carers at LOCF endpoint.
Conclusion: Reducing the frequency of antipsychotic medication administration in stable patients with schizophrenia by switching from PP1M to PP3M may reduce carer burden.

1. Introduction

The burden experienced by carers of patients with schizophrenia is often underestimated. This burden can be emotional, with carers feeling isolated, anxious and depressed; physical, through sleep disturbances and worsening health; social, due to increased caring workload and decreased leisure time and social interaction; and financial due to increased household expenditure, healthcare and travel costs, and loss of earnings for carers [1–9].

Up to around half of patients with schizophrenia in Western countries live with their carers and depend on their assistance, while in Asian countries, this can be as high as 70% [5,7,10]. The relationships between the carer and the person with schizophrenia may deteriorate for many reasons, including strained interactions, an increase in stress-related family arguments, loss of social contact outside the family and lack of understanding by family members, neighbours and friends [5,7,9].

Carer burden increases when caring for patients with severe or persistent schizophrenia and those with suboptimal treatment adherence [8,11,12], which is common in patients taking daily oral antipsychotic medication [13–16]. Suboptimal treatment adherence is associated

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with poorer patient outcomes, including an increased risk of relapse or hospitalisation of patients with schizophrenia [17,18] and, thus, an increase in carer burden.

Long-acting injectable antipsychotic treatments (LATs) have been developed to overcome the need for patients with schizophrenia to take daily oral antipsychotic medication. LATs are a valuable treatment option that enhance treatment continuation [16,17], with the potential to improve patient outcomes and, subsequently, reduce carer burden. LATs allow patients, carers and physicians to shift their focus from daily reminders about taking medication to other important aspects of patient health, including psychosocial treatment, substance abuse treatment, smoking cessation, health maintenance and vocational rehabilitation [19].

Paliperidone palmitate 3-monthly (PP3M) is a LAT formulation approved for maintenance treatment of schizophrenia in patients previously stabilised with paliperidone palmitate 1-monthly (PP1M) [20]. A pooled analysis of two double-blind, randomised, phase 3 studies has shown that switching from oral antipsychotic treatment to PP1M and subsequently to PP3M significantly reduced carer burden, with improvements significantly correlated with relapse status, patient age and age at diagnosis ($P < 0.001$) [19]. However, as with all randomised controlled trials (RCTs), these studies had stringent eligibility criteria and, as a result, the patients included were not typically representative of the broader patient population in real-life clinical practice.

Collection of data from pragmatic clinical trials therefore provides valuable complementary data to that obtained from RCTs. As such, carer burden has recently been analysed as part of a prospective, single-arm, non-randomised, open-label, international, multicentre study in patients with schizophrenia who transitioned from PP1M to PP3M treatment in a clinical practice setting (ClinicalTrials.gov identifier NCT02713282; EudraCT number 2015–004835-10; also known as REMISSIO). 95.4% of the patients (291/305) completed the 52-week study. 56.8% of patients (95% confidence interval [CI]: 51.0, 62.4) achieved the primary efficacy endpoint of symptomatic remission (defined using the two-dimensional Andreasen criteria: (1) symptom severity criterion: all eight selected Positive and Negative Syndrome Scale (PANSS) score of mild or better (≤3); (2) duration criterion: the 8 selected item scores remain ≤3 for a minimum of 6 months) at last observation carried forward (LOCF) endpoint. Following treatment with PP3M, 31.8% achieved symptomatic and functional remission (Personal and Social Performance [PSP] scale total score >70) at LOCF endpoint [21,22].

Carer burden was assessed using the validated Involvement Evaluation Questionnaire (IEQ) [23]. The IEQ was selected because it includes a broad range of domains of caregiving consequences, is easy to administer, has data to support its reliability and is validated for use specifically in schizophrenia in a number of languages. The primary manuscript reported an overall reduction in carer burden at LOCF endpoint compared with baseline [22]. This article further explores the impact of PP3M treatment on carers of patients with schizophrenia from this study.

2. Methods

The methods for this study have been published in detail [22]. In brief, patients aged 18–50 years with a diagnosis of schizophrenia [24] previously stabilised with PP1M treatment were transitioned to PP3M (in line with the approved license). Patients were eligible for inclusion if they were adequately treated with PP1M (50–150 mg eq.) for ≥ 4 months (with two identical doses before switching) and had a baseline PANSS total score of <70 (for exclusion criteria see Garcia-Portilla, 2020 [22]). Following a 7-day screening period, patients transitioned from PP1M (50–150 mg eq.) to PP3M (175–525 mg eq.), and then entered a 52-week, flexible-dose treatment period.

Carer burden was assessed for a patient's designated carer, who was mutually agreed upon by the patient and the study investigator. Carers included family members, friends or significant others who had at least 1 h of contact with the patient per week but could not be a paid carer. All carers must have been willing to complete the required IEQ assessments. The same carer completed the assessments throughout the study and attended clinic visits during which the IEQ was completed.

The study protocol and amendments underwent ethics committee review at each study site. The study was conducted in compliance with the Declaration of Helsinki and was consistent with Good Clinical Practice and applicable regulatory requirements. Written informed consent was obtained from all patients before enrolment. The designated carer signed a separate informed consent form (ICF) prior to the first baseline assessment; patients were able to take the ICF home to discuss it with potential carers prior to signing.

2.1. Assessment of carer burden

Carer burden was assessed as a secondary endpoint using the IEQ [23]. The full IEQ (European Version) was used in this study, consisting of 81 items across seven modules: 15 items on the socio-demographics of the patient and their family and contact variables between patient and carer, such as household composition (Module 1; items 1–15); 31 items on carer consequences of psychiatric disorders (Module 2; items 16–46); eight items on extra financial expenses incurred on behalf of the patient (Module 3; items 47–54); a 12-item General Health Questionnaire (GHQ) as a measure of the carer's distress (Module 4; items 55–66); three items on the carer's use of professional help (Module 5; items 67–69); 11 items on the consequences for the patient's children (Module 6; items 70–80); and an open question for additional comments (Module 7; item 81).

Module 2 is the IEQ core module. It is designed to measure consequences of caring for a patient with schizophrenia on family members and friends, with a recall period for each question of the last 4 weeks [23]. Items in Module 2 relate to the encouragement and care that the carer provides for the patient, personal problems between the patient and carer and the carer's worries, ability to cope and subjective burden. Module 2 can be subdivided into four domains (tension, supervision, worrying and urging) and a total score can be calculated (Fig. 1).

The IEQ was completed by the designated carer at Day 1 (baseline), and at the Month 6 and 12 visits. A visit window of ± 2 days was allowed for the carer and the patient on Day 1 and ± 14 days was permitted at Months 6 and 12.

2.2. Statistical analysis

The carer analysis set consisted of all enrolled patients who received ≥1 PP3M administration with a participating carer. In addition to observed case analysis, endpoint analysis using the LOCF method was performed.

For IEQ Module 2, items were rated on a 5-point Likert scale to create a value for each domain and a total score (Fig. 1), with higher values indicating higher levels of carer burden. The change from baseline at LOCF endpoint in Module 2 total and individual domain values were summarised for carers in the total analysis group and in the following subgroups of patients: with versus without symptomatic remission at LOCF endpoint; time to diagnosis of >3 years versus ≤3 years; 4–-6 months versus >6 months on previous PP1M; and a switch to PP3M from PP1M monotherapy versus polytherapy (polytherapy was defined as use of PP1M plus at least one other psychotropic therapy in the period just preceding PP3M start). The four domain scores and the total IEQ scores were summarised using descriptive statistics including the 95% CI and the percentage of carers per answer. As the scoring ranges of the domains differed, percentage improvement from baseline to LOCF endpoint was also calculated to enable comparison among the four domains.

Spearman's correlation was used to explore the relationship between baseline and LOCF endpoint IEQ parameter values (IEQ total and domain scores and GHQ) and baseline demographics and disease

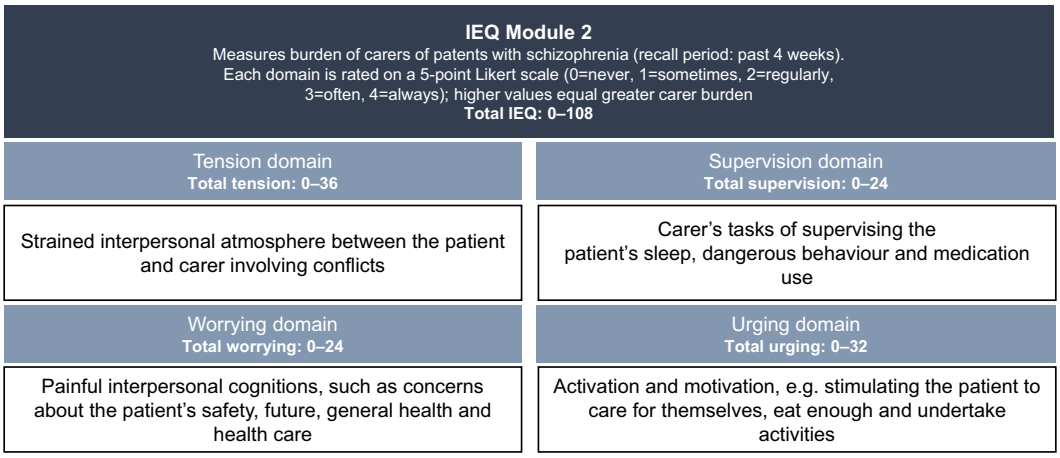


Fig. 1. IEQ Module 2 (core module). It should be noted that the total IEQ score is not a sum of the four domains as some items occur within more than one domain. IEQ, Involvement Evaluation Questionnaire.

characteristics, as well as baseline, LOCF endpoint and change from baseline values of efficacy endpoints reflecting disease severity and functioning. Efficacy (including 95% CIs) results were analysed descriptively, no statistical hypothesis testing was carried out.

To investigate factors affecting the carer burden at baseline and at LOCF endpoint, exploratory, stepwise linear regression analysis was performed taking the IEQ total and domain scores and GHQ as dependent values. The factors assessed were remission symptom severity criteria (eight PANSS items ≤3) met at baseline (yes/no); symptomatic remission (eight PANSS items ≤3 for at least 6 months) at LOCF endpoint (yes/no); factors relating to patient and carer demographics, for example, whether the patient was part of the carer's household (yes/no); and patient disease characteristics (duration, concomitant medications, disease severity [Clinical Global Impression], symptoms [PANSS positive, negative and total scores] and functioning [PSP scale]).

3. Results

The overall outcomes of the REMISSIO study have been published in detail previously [22]. Of the 305 patients included in the study, a total of 174 carers were identified, of which 159 carers (91%) participated in the study and completed the IEQ (having a carer/carer participation was not an inclusion criterion for the study). Carers were most likely to be a parent, spouse or partner, or sibling of the patient, most patients were part of the carer's household and half of carers had more than 32 h of contact with the patient per week at baseline. Carer baseline characteristics are provided in Table 1. Drop-out rate of patients with carers completing IEQ was 1,2% ($n = 2$), somewhat below the overall drop-out rate of the parent study (4,6% [22]).

3.1. Key carer outcomes (IEQ Module 2)

Mean (SD) IEQ Module 2 total score at baseline was in the lower range, 23.8 (12.6), reflecting the stabilisation of patients on PP1M treatment prior to switching to PP3M. At LOCF endpoint, the total score decreased by mean (SD) 4.0 (12.2), the 95% CI not including the zero, indicating a significant overall reduction in carer burden, (95% CI: −5.9, −2.1) (Table 2, Fig. 2). Baseline scores varied across the four domains, being highest for the worrying domain and lowest for supervision (Fig. 2). Statistically significant improvements were observed in three of the four Module 2 domains — supervision, urging and worrying — numerical improvements were observed in the tension domain (Table 2, Fig. 2).

The distribution of values for each of the domains at baseline and LOCF endpoint are presented in Fig. 3. The distribution moved towards lower values at LOCF endpoint compared with baseline for all domains.

Fig. 4 presents six specific IEQ items indicating greatest carer burden at baseline, based on the highest percentage of responses of 'regularly', 'often' or '(almost) always'. These six items were found in two domains: urging and worrying. The percentage of carers who answered 'regularly', 'often' or '(almost) always' decreased across these six specific items from baseline to LOCF endpoint, indicating that carer burden was decreased after switching to PP3M.

3.2. Total IEQ Module 2 outcomes per patient subgroup

Table 2 presents changes in IEQ Module 2 total and domain values from baseline to LOCF endpoint by patient subgroup. Improvements in the burden of carers from baseline to LOCF endpoint of different magnitudes were observed in all subgroups.

For carers of patients with recently diagnosed schizophrenia (≤3 years), the baseline total IEQ scores were somewhat lower than those for carers of patients who were diagnosed with schizophrenia >3 years ago. At LOCF endpoint, an improvement in the total IEQ score was observed for carers of patients who were diagnosed >3 years ago, but not for carers of recently diagnosed patients. The carers of patients who switched from PP1M polytherapy to PP3M had the largest numerical improvement in total IEQ scores; however, given the wide CI due to the small sample size ($n = 28$), this difference was not statistically significant (Table 2).

For the six IEQ Module 2 items for which greatest baseline carer burden was reported, carers of patients who did not achieve symptomatic remission at LOCF endpoint answered 'regularly', 'often' or '(almost) always' more frequently than carers of patients who achieved symptomatic remission (Fig. 4). At LOCF endpoint, the percentage of carers who rated 'regularly', 'often' or '(almost) always' had decreased considerably compared with baseline for all six items both for carers of patients who achieved symptomatic remission at LOCF endpoint and carers of those who did not. For items in the urging domain, the magnitude of change was larger for carers of patients who did not achieve symptomatic remission than for carers of patients achieving symptomatic remission. In contrast, for items in the worrying domain, the magnitude of change from baseline was similar in the two groups.

3.3. Additional results from other IEQ modules

Financial expenses incurred by carers (IEQ Module 3) did not substantially change from baseline to LOCF endpoint, except for fewer

Table 1
Baseline characteristics of carers who completed the IEQ and the patients they care for.

		LOCF endpoint symptomatic remission	
	Total group[a] ($N = 305$)	Yes ($n = 172$)	No ($n = 131$)
Patient age, years			
n[b]	159	88	71
Mean (SD)	37.0 (9.2)	37.4 (10.1)	36.5 (7.9)
Median	36	35.5	38
Range	(20; 77)	(20; 77)	(21; 54)
Patient sex, *n* (%)			
n[b]	159	88	71
Male	102 (64.2)	50 (56.8)	52 (73.2)
Female	57 (35.8)	38 (43.2)	19 (26.8)
Time since diagnosis, years			
n[b]	157	87	70
Mean (SD)	9.4 (7.3)	9.1 (6.8)	9.6 (7.8)
Median	7.0	7.0	7.5
Range	(0; 35)	(0; 25)	(1; 35)
Carer age, years			
n[c]	159	88	71
Mean (SD)	54.8 (12.8)	53.5 (12.8)	56.5 (12.5)
Median	56.0	55.5	59.0
Range	(20; 84)	(20; 83)	(24; 84)
Carer sex, *n* (%)			
n[c]	159	88	71
Male	75 (47.2)	42 (47.7)	33 (46.5)
Female	84 (52.8)	46 (52.3)	38 (53.5)
Carer civil status, *n* (%)			
n[c]	159	88	71
Single	14 (8.8)	9 (10.2)	5 (7.0)
Married/long-term relationship	110 (69.2)	60 (68.2)	50 (70.4)
Divorced	18 (11.3)	11 (12.5)	7 (9.9)
Widowed	17 (10.7)	8 (9.1)	9 (12.7)
Carer relationship with the patient, *n* (%)			
n[c]	159	88	71
Parent	83 (52.2)	41 (46.6)	42 (59.2)
Daughter/son	12 (7.5)	6 (6.8)	6 (8.5)
Sibling	24 (15.1)	16 (18.2)	8 (11.3)
Other relative	4 (2.5)	3 (3.4)	1 (1.4)
Spouse/partner	26 (16.4)	18 (20.5)	8 (11.3)
Friend	3 (1.9)	2 (2.3)	1 (1.4)
Other	7 (4.4)	2 (2.3)	5 (7.0)
Patient part of carer's household, *n* (%)			
n[c]	159	88	71
No	40 (25.2)	24 (27.3)	16 (22.5)
Yes	119 (74.8)	64 (72.7)	55 (77.5)
Average weekly contact with the patient, *n* (%)			
n[c]	159	88	71
<1 h/week[d]	14 (8.8)	8 (9.1)	6 (8.5)
1–4 h/week	24 (15.1)	16 (18.2)	8 (11.3)
5–8 h/week	9 (5.7)	5 (5.7)	4 (5.6)
9–16 h/week	11 (6.9)	6 (6.8)	5 (7.0)
17–32 h/week	15 (9.4)	9 (10.2)	6 (8.5)
>32 h/week	86 (54.1)	44 (50.0)	42 (59.2)

[a] Total number of patients randomised.
[b] Number of patients with a participating carer.
[c] Number of carers.
[d] Whilst the inclusion criteria required the carer to have ≥1 h of contact with the patient per week, 14 patients reported ≤1 h on average per week, therefore these should be considered as protocol deviations. IEQ, Involvement Evaluation Questionnaire; LOCF, last observation carried forward; SD, standard deviation.

carers incurring medicine costs at LOCF endpoint compared with baseline (Online Resource 1). Similar results were noted irrespective of whether the patient was in symptomatic remission or not at LOCF endpoint.

Carers reported a trend towards improvement in some of the items relating to carers' general health at LOCF endpoint compared with baseline including improved concentration, sleep and confidence (Online resource 2). Further, general health scores at baseline and LOCF endpoint were lower for carers of patients who did not reach symptomatic remission compared with those in remission; however, there was still a shift towards improvement in this group compared with baseline. Less strain, improved ability to overcome difficulties and decreased unhappiness were also reported by carers of patients who achieved symptomatic remission at LOCF endpoint (Supplemental materials, Online resource 2).

Use of professional help by carers (Module 5) did not substantially change from baseline to LOCF endpoint, although more carers used medication (any) at LOCF endpoint than at baseline across all subgroups (Supplemental materials, Online resource 3). Thirty-one patients (19.6%) had children; 21 patients had at least one child under the age of 16 years. Little impact was seen on the children of patients at baseline or LOCF endpoint (Module 6; Supplemental materials, Online resource 4).

3.4. Relationship between carer burden and patient demographics and disease characteristics

Achievement of functional remission during PP3M treatment, defined as PSP score >70, was associated with lower carer burden. Carers of patients who achieved functional remission during PP3M treatment had considerably lower IEQ total scores (mean [95% CI]) versus carers of patients who did not achieve functional remission, both at baseline (18.1 [15.4, 20.7] versus 26.4 [24.00, 28.9], respectively) and LOCF endpoint (16.4 [14.5, 18.4] versus 21.9 [19.5, 24.4], respectively). The results were similar for the supervision and urging domains, however, in the worrying domain, this was only observed at baseline. At baseline, higher carer burden was observed if patients were part of the same household; this difference in burden was numerically consistent across the four domains (at baseline and LOCF endpoint) however, only the baseline mean of the urging domain showed non-overlapping 95% CIs. At baseline, there was no correlation between IEQ scores and sex of the carer or patient, patient age or disease duration. There were also no correlations between IEQ scores and these parameters at LOCF endpoint, except weak negative correlations between disease duration and worrying and GHQ.

At baseline, there were weak positive correlations (all correlation coefficients [Rs] varying from 0.23 to 0.28) between IEQ total scores and PANSS total and positive scores, worrying and PANSS positive score and urging and PANSS total, negative and general scores. This indicates that higher PANSS scores may be weakly associated with higher IEQ scores, but the correlations do not allow any definitive conclusions to be drawn. There were no correlations between IEQ and PANSS scores at LOCF endpoint.

In multiple linear regression analyses, factors associated with higher carer burden at baseline were patients being part of the carer's household (particularly in the urging domain); being a male carer (urging domain only); higher carer age (worrying domain only); and additional use of psychotropic medication (particularly in the supervision domain). Use of concomitant psychotropic medication by the patient was also associated with higher carer distress and carer burden at LOCF endpoint, especially in the urging and supervision domains (Table 3). Patients being in functional remission at baseline was associated with lower baseline carer burden. The model fit (r-squared) varied from 0.06 to 0.36.

4. Discussion

IEQ assessments as part of the REMISSIO study indicate that the carer burden was mild to moderate at baseline for patients stabilised on PP1M prior to the start of the study (mean [SD] IEQ total: 23.8 [12.5]). Additionally, the main findings from these analyses show that continuing to treat an already stable patient with PP3M further reduces their carer's burden.

Baseline scores were highest in the worrying domain, demonstrating the subjective component of carer burden in schizophrenia. Carer burden was lower if patients achieved functional remission and was

Table 2
Change in IEQ Module 2 total and domain values for carers across specific patient subgroups between baseline and LOCF endpoint.

	Total group	Symptomatic remission at LOCF endpoint		Time to diagnosis		Previous PP1M		Switch to PP3M from PP1M monotherapy/polytherapy	
		Yes	No	≤3 years	>3 years	4–6 months	>6 months	Monotherapy	Polytherapy
Total scores									
n	158	88	70	36	122	33	123	130	28
Baseline, mean (SD)	23.8 (12.6)	22.8 (13.2)	25.0 (11.6)	22.2 (9.1)	24.3 (13.4)	24.5 (12.6)	23.5 (12.6)	22.5 (11.2)	29.8 (16.4)
LOCF, mean (SD)	19.8 (10.9)	19.0 (10.9)	20.7 (10.9)	20.2 (8.1)	19.6 (11.6)	20.1 (13.5)	19.7 (10.2)	19.2 (9.7)	22.5 (15.3)
Change, mean (SD)	−4.02 (12.2)	−3.8 (12.0)	−4.3 (12.5)	−2.0 (12.8)	−4.6 (12.0)	−4.4 (11.6)	−3.8 (12.4)	−3.3 (11.2)	−7.3 (15.8)
95% CI	−5.9, −2.1	−6.4, −1.3	−7.3, −1.3	−6.3, 2.4	−6.8, −2.5	−8.5, −0.3	−6.0, −1.6	−5.3, −1.4	−13.5, −1.2
Tension									
n	158	88	70	36	122	33	123	130	28
Baseline, mean (SD)	8.2 (3.0)	8.2 (3.0)	8.2 (3.1)	7.6 (2.9)	8.4 (3.1)	8.5 (3.7)	8.1 (2.9)	8.0 (2.7)	9.0 (4.2)
LOCF, mean (SD)	7.9 (2.9)	7.8 (2.6)	8.0 (3.3)	7.9 (2.3)	7.9 (3.1)	8.3 (3.8)	7.8 (2.7)	7.9 (2.8)	7.8 (3.6)
Change, mean (SD)	−0.3 (3.5)	−0.4 (3.1)	−0.2 (4.1)	0.2 (2.9)	−0.5 (3.7)	−0.2 (4.1)	−0.3 (3.4)	−0.1 (3.4)	−1.2 (4.2)
95% CI	−0.9, 0.3	−1.0, 0.3	−1.2, 0.8	−0.8, 1.2	−1.1, 0.2	−1.6, 1.3	−1.0, 0.3	−0.7, 0.5	−2.8, 0.5
Supervision									
n	144	80	64	32	112	31	111	118	26
Baseline, mean (SD)	3.4 (3.6)	3.31 (3.8)	3.5 (3.3)	3.0 (3.4)	3.5 (3.7)	3.2 (3.6)	3.4 (3.7)	3.0 (3.2)	5.1 (5.0)
LOCF, mean (SD)	2.3 (2.8)	2.2 (3.1)	2.4 (2.6)	2.4 (2.3)	2.2 (3.0)	2.4 (3.4)	2.3 (2.7)	2.1 (2.6)	3.3 (3.7)
Change, mean (SD)	−1.1 (3.6)	−1.1 (4.0)	−1.1 (3.2)	−0.6 (4.2)	−1.3 (3.4)	−0.8 (3.3)	−1.2 (3.7)	−1.0 (3.2)	−1.8 (5.3)
95% CI	−1.7, −0.5	−2.0, −0.2	−1.9, −0.3	−2.1, 1.0	−1.9, −0.6	−2.0, 0.4	−1.9, −0.5	−1.6, −0.4	−3.9, 0.4
Worrying									
n	158	88	70	36	122	33	123	130	28
Baseline, mean (SD)	10.5 (4.8)	9.9 (4.7)	11.2 (4.9)	10.1 (4.2)	10.6 (5.0)	10.8 (5.4)	10.4 (4.7)	10.3 (4.6)	11.4 (5.6)
LOCF, mean (SD)	8.8 (4.1)	8.1 (3.4)	9.7 (4.7)	9.3 (3.1)	8.7 (4.4)	8.9 (4.5)	8.8 (4.1)	8.8 (3.8)	9.1 (5.5)
Change, mean (SD)	−1.7 (4.5)	−1.8 (4.1)	−1.5 (4.9)	−0.8 (4.6)	−1.9 (4.4)	−2.0 (4.8)	−1.5 (4.4)	−1.5 (4.2)	−2.3 (5.6)
95% CI	−2.3, −0.9	−2.7, −0.9	−2.6, −0.3	−2.3, 0.8	−2.7, −1.1	−3.7, −0.3	−2.3, −0.8	−2.2, −0.8	−4.5, −0.1
Urging									
n	144	80	64	32	112	31	111	118	26
Baseline, mean (SD)	6.8 (5.7)	6.5 (5.8)	7.2 (5.4)	6.4 (3.7)	6.9 (6.1)	6.7 (4.8)	6.8 (5.9)	6.1 (5.3)	9.8 (6.5)
LOCF, mean (SD)	4.8 (4.3)	4.9 (4.8)	4.7 (3.7)	4.3 (4.0)	4.9 (4.4)	4.4 (4.4)	4.9 (4.3)	4.4 (3.8)	6.7 (5.7)
Change, mean (SD)	−2.0 (5.5)	−1.6 (5.5)	−2.6 (5.4)	−2.1 (4.7)	−2.0 (5.7)	−2.3 (3.8)	−1.9 (5.9)	−1.8 (5.3)	−3.1 (6.1)
95% CI	−2.9, −1.1	−2.8, −0.3	−3.9, −1.2	−3.8, −0.4	−3.0, −0.9	−3.6, −0.9	−3.0, −0.8	−2.7, −0.8	−5.5, −0.6

CI, confidence interval; IEQ, Involvement Evaluation Questionnaire; LOCF, last observation carried forward; PP1M, paliperidone palmitate 1-monthly; PP3M, paliperidone palmitate 3-monthly; SD, standard deviation.

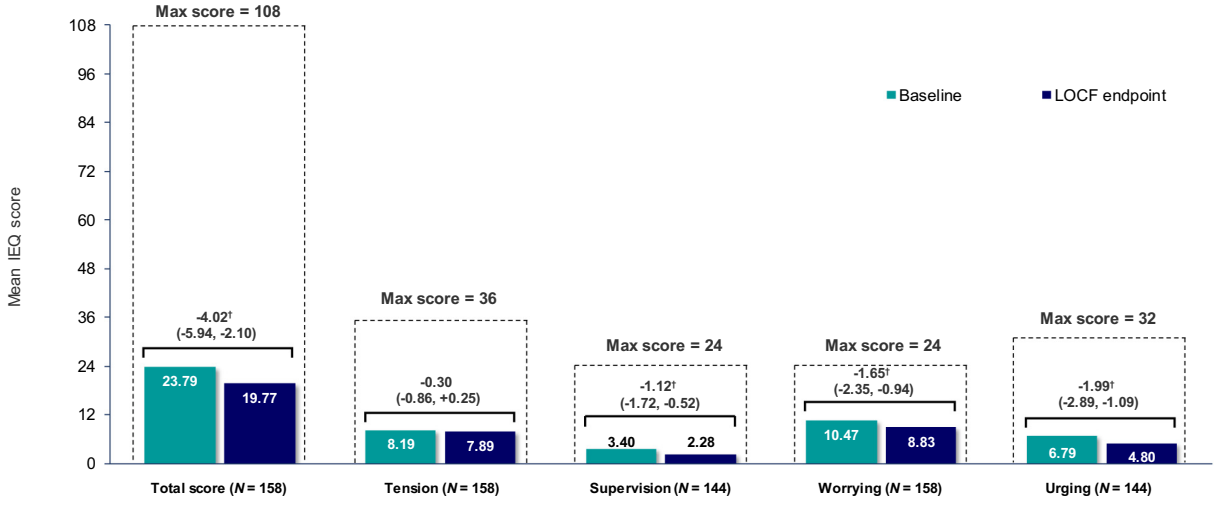
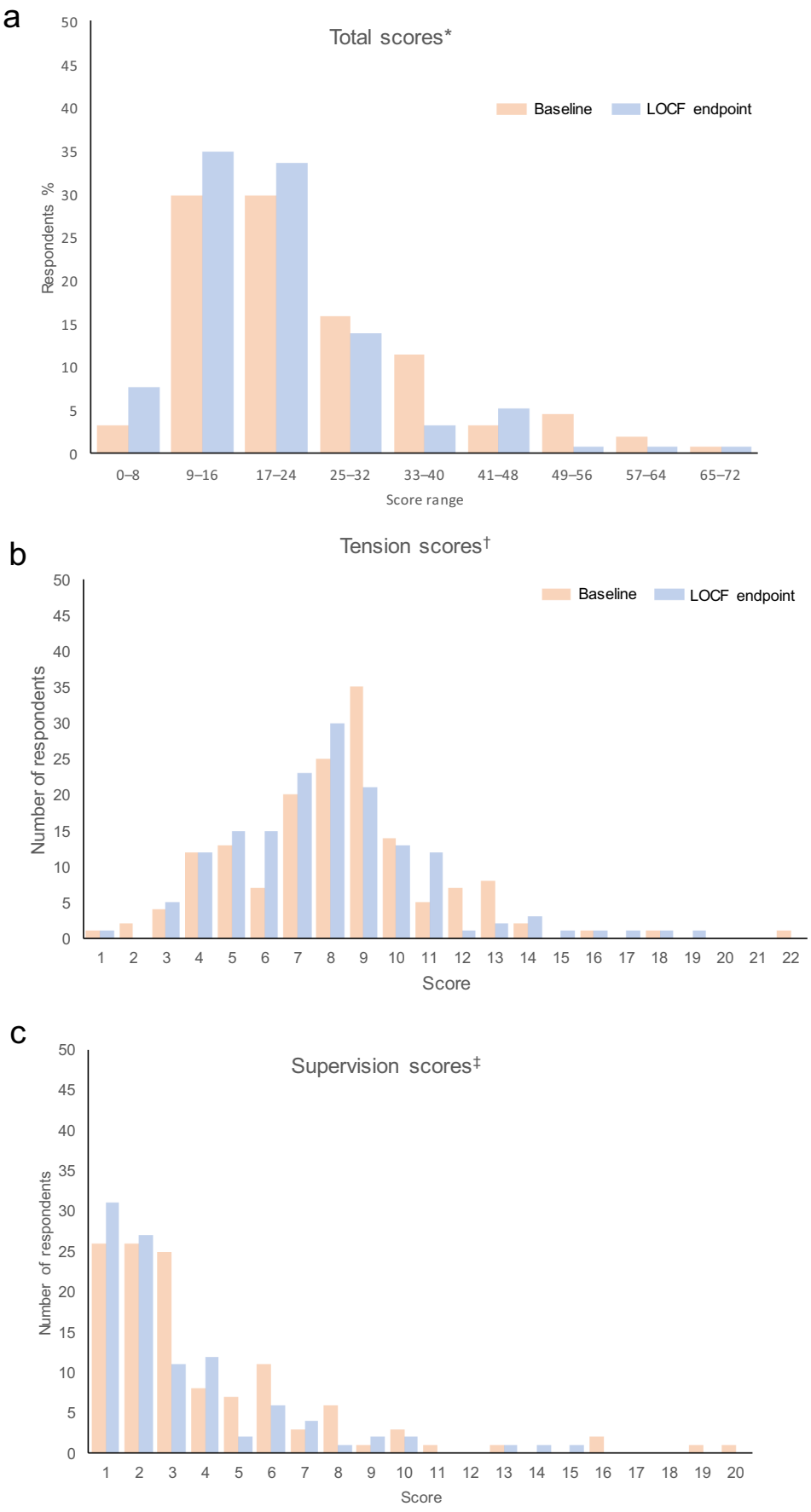


Fig. 2. Change (95% CI) in total IEQ and four domain values for core Module 2 between baseline and endpoint* for carers of patients in the study. *In cases where an endpoint value was missing, the last assessed value was imputed (LOCF). †$P < 0.0001$. IEQ, Involvement Evaluation Questionnaire; LOCF, last observation carried forward.

higher if patients were part of the carers household or were receiving additional psychotropic medications. Nonetheless, carer burden improved following a switch from PP1M to PP3M in the current study. This is consistent with results from the pooled analysis of RCTs, which showed meaningful and significant improvement of carer burden after patients switched to PP3M [19].

Improvement in burden scores were observed for the carers in the subgroups of patients analysed in this study: patients who did achieve symptomatic response at LOCF endpoint versus those that did not; those with recently diagnosed schizophrenia (≤3 years) versus those diagnosed >3 years ago; patients previously treated with PP1M for 4–-6 months versus those treated for >6 months; and patients who


a
Total scores*
Baseline
LOCF endpoint
Respondents %
0–8
9–16
17–24
25–32
33–40
41–48
49–56
57–64
65–72
Score range
b
Tension scores†
Baseline
LOCF endpoint
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Score
c
Supervision scores‡
Number of respondents
Score

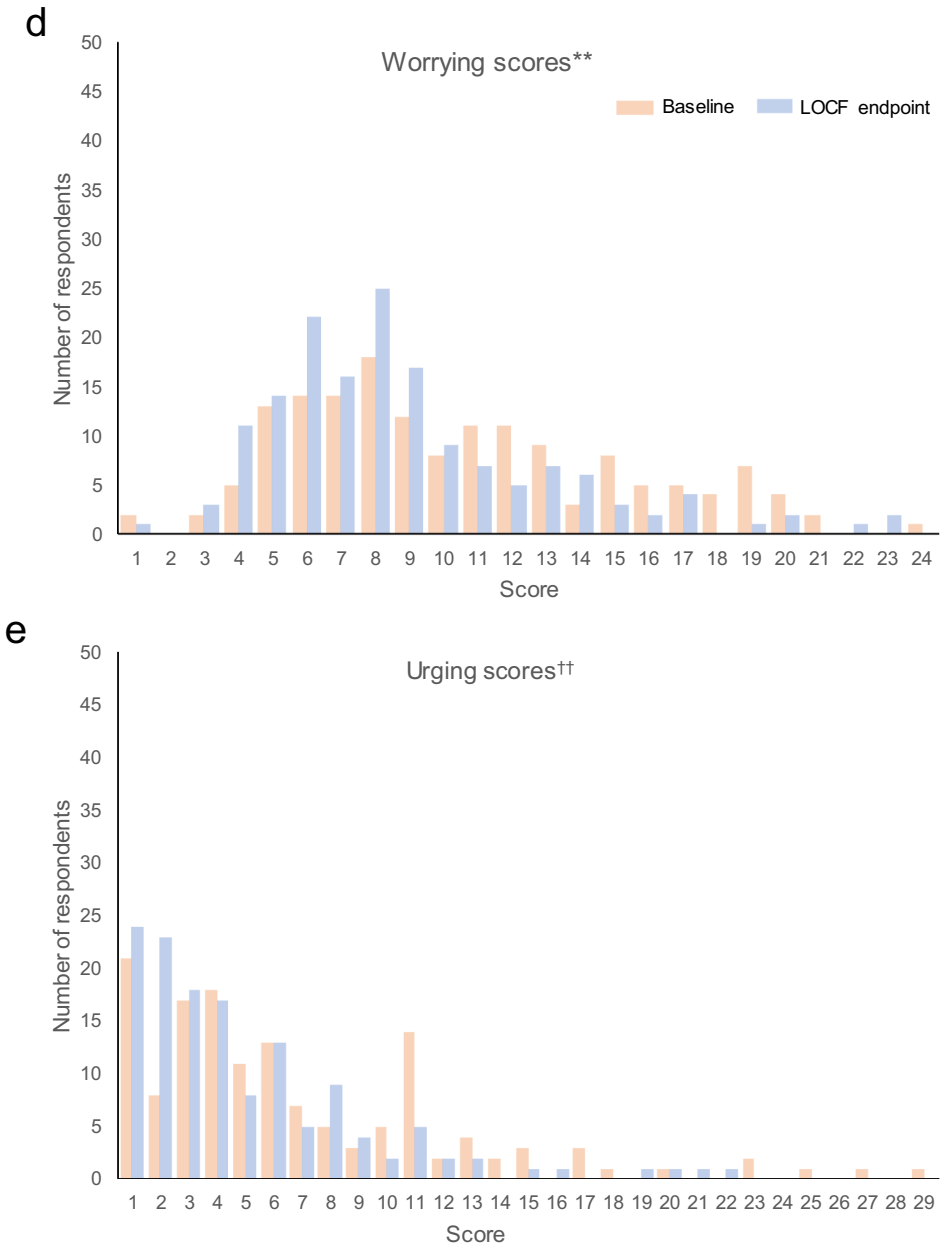

Fig. 3. a Total scores; b Tension scores; c Supervision scores; d Worrying scores; e Urging scores. The distribution of values at baseline and LOCF endpoint for the total IEQ (a), tension (b), supervision (c), worrying (d) and urging (e) domains of Module 2 *Maximum possible score 108. †Maximum possible score 36; no scores >22 at either time point. ‡Maximum possible score 24; no scores of >20 at either time point. **Maximum possible score 24. ††Maximum possible score 32; no scores of >29 at either time point. IEQ, Involvement Evaluation Questionnaire; LOCF, last observation carried forward.

switched to PP3M from PP1M monotherapy versus PP1M polytherapy. Each of these subgroups consistently demonstrated improvements in IEQ. The carers of patients who switched from PP1M polytherapy to PP3M had the largest decrease in IEQ score. This suggests that switching from PP1M to PP3M, with a less frequent dosing schedule, is beneficial to the carer as well as the patient.

There is limited information within the literature to quantitatively assess the clinical relevance of these results. Li et al. (2018) reported that a reduction in IEQ total score of ≥6 was considered a reasonable estimate of reduced carer burden after 13 weeks' treatment with PP1M; this would equate to a 19% reduction based on a mean baseline score of 30.98 (SD: 15.50) [25]. Applying these criteria to the current study, a reduction of ≥6 in IEQ total score was not reached at 52 weeks (reduction 4.02), although the relative reduction of 17% in the current study approached that of Li et al. (2018) despite lower baseline IEQ total scores indicating less severe carer burden (23.79 [SD:12.55]). It is also important to note that patients in the Li et al. (2018) study showed higher symptom expression at baseline (PANSS total score of ≥70) than those in the current study (PANSS total score < 70), in which patients' symptoms were adequately controlled on PP1M. In another study, Parabiaghi et al. (2007) defined improvement and worsening of carer burden as a change of ±0.5 in IEQ domain scores; however, they did not provide any justification for the use of this cut-off [26]. Further, Gopal et al. reported a significant overall improvement of 8.9 points in carer IEQ score for patients who switched from an oral antipsychotic to PP1M or PP3M, in addition to reduced impact on leisure time and fewer hours spent caring. These changes were considered to indicate meaningful improvement in carer burden [19].

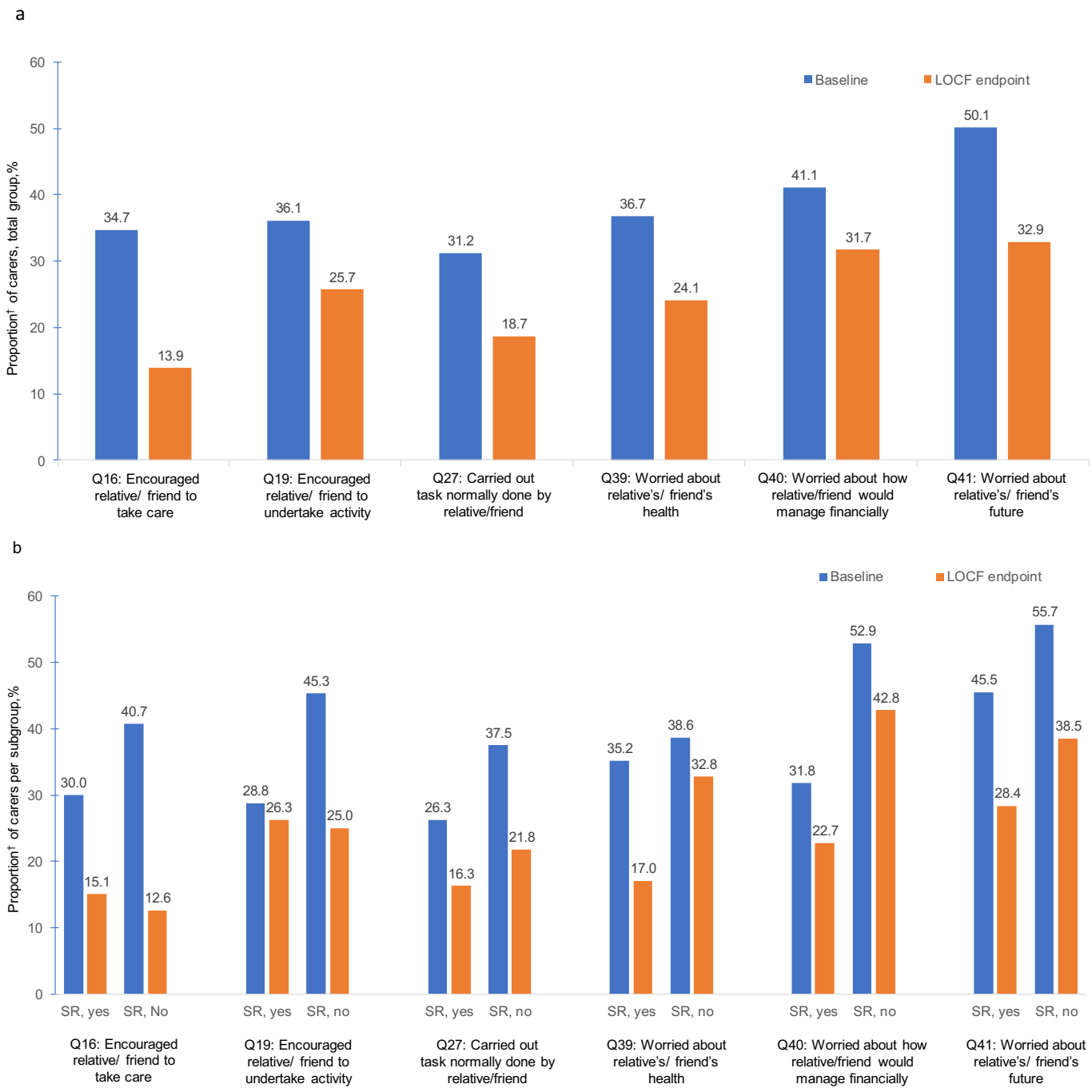

Fig. 4. Proportion of carers answering 'regularly', 'often' or '(almost) always' to select questions from Module 2* at baseline and LOCF endpoint for the total group (a) and subgroups who did or did not achieve symptomatic remission at LOCF endpoint (b). *Questions were selected based on the highest proportion of patients answering 'regularly', 'often' or '(almost) always' at baseline. †Sum of the percentages for the responses 'regularly', 'often' and '(almost) always'. LOCF, last observation carried forward; SR, symptomatic remission (at LOCF endpoint).

Data from the long-term CATIE study, in which patients had been living with schizophrenia for an average of 13 years, suggested that changes in pharmacological interventions had little effect on family and carer burden (assessed by a different questionnaire: Family Experience Interview Schedule) [27]. Medications used included oral, first-generation (perphenazine) and second-generation (olanzapine, quetiapine, risperidone or ziprasidone) antipsychotics. Nonadherence to oral medications is high and has been shown to have a substantial effect on carer burden [11,12]. Given that LATs improve treatment continuation and patient outcomes [28–31], they may have a greater effect on improving carer burden. Unfortunately, information regarding whether patients had a history of nonadherence was not captured during the current study, but this would be interesting to explore in the future. Nonetheless, despite the observed differences in demographics and methodology versus the current study results from CATIE serve to contextualise the current results in two ways. Firstly, they highlight the importance of achieving early symptom control and continuous treatment to minimise carer burden. Secondly, they highlight that psychosocial interventions aimed at the carer are also important to alleviate carer burden. This should be remembered even in the context of reduced carer burden with LATs.

Carers' wellbeing is essential for the optimal care of patients with schizophrenia and is substantially impacted by the emotional distress,

Table 3
Results from stepwise linear regression modelling to investigate factors that affect IEQ total and domain scores at baseline and at LOCF endpoint.

IEQ dependent variable	Significant factors included in the model	Regression coefficient	Beta coefficient	*p*-value	r-squared
IEQ Module 2 total					
Baseline	Part of household	4.48	0.16	0.0366	0.18
	Baseline PSP >70	−6.70	−0.25	0.0022	
	Baseline use of psychotropics	3.79	0.15	0.0453	
LOCF endpoint	Baseline IEQ sum score	0.37	0.42	<0.0001	0.31
	Concomitant use of psychotropics	5.73	0.22	0.0017	
Tension					
Baseline	Baseline PSP >70	−1.23	−0.19	0.0175	0.06
LOCF endpoint	Baseline IEQ tension score	0.25	0.26	0.0014	0.13
Supervision					
Baseline	Baseline PSP >70	−1.80	−0.25	0.0027	0.18
	Baseline use of psychotropics	1.11	0.16	0.0431	
LOCF endpoint	Baseline IEQ supervision score	0.34	0.40	<0.0001	0.27
	Concomitant use of psychotropics	1.24	0.19	0.0154	
	LOCF PANSS general score	0.08	0.15	0.0464	
Worrying					
Baseline	Carer age	0.07	0.18	0.0181	0.13
LOCF endpoint	Baseline IEQ worrying score	0.41	0.48	<0.0001	0.32
Urging					
Baseline	Carer sex	2.09	0.18	0.0199	0.16
	Part of household	2.18	0.17	0.0335	
	Baseline PSP >70	−3.27	−0.27	0.0009	
LOCF endpoint	Baseline IEQ urging score	0.29	0.38	<0.0001	0.26
	LOCF CGI-S	0.79	0.16	0.0314	
	Concomitant use of psychotropics	2.24	0.22	0.0031	
GHQ Module 4 sum score					
Baseline	No significant effects				
LOCF endpoint	Baseline IEQ GHQ sum score	0.33	0.38	<0.0001	0.36
	LOCF PANSS negative score	−0.07	−0.18	0.0119	
	Concomitant use of psychotropics	1.00	0.22	0.0022	
	LOCF CGI-C	0.33	0.15	0.0440	

CGI-C, Clinical Global Impression-Change; CGI—S, Clinical Global Impression-Severity; GHQ, General Health Questionnaire; IEQ, Involvement Evaluation Questionnaire; LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance.

health issues, social isolation and financial pressures associated with caring for a person with schizophrenia [1–9]. However, carer quality of life (QoL) is only partially dependent on the patient's disease state, with one study showing that, of the patient-related characteristics evaluated, only the duration of the patient's schizophrenia was related to carer QoL, accounting for 9% of variance in QoL [32]. While the current study did not observe correlation between disease duration and carer burden at baseline, there was weak negative correlation between disease duration and worry and carer's general health at LOCF endpoint. Furthermore, the current study found only weak correlation between the IEQ values in the worrying domain and patient symptom level, demonstrating that carer burden is not solely dependent on the patient's disease state, but is also impacted by the carer's coping skills.

In addition to patient characteristics, psychosocial aspects such as the carer's own self-esteem, social support and psychosocial functioning, including their perceived independence and ability to attain their own life goals, also have a large impact on carer QoL [32]. Furthermore, carer QoL appears to be dependent on whether the carer lives in the same household as the person with schizophrenia, with carers living separately experiencing greater QoL, possibly because they feel more in control of their own direction in life [32]. This was reflected in the current study, with higher carer burden at baseline, particularly in the urging domain, when the patient was part of the carer's household. Thus, the potential impact of a 3-monthly LAT on helping carers to gain independence and confidence in achieving their own goals is of interest, particularly given that PP3M may help to shift the focus of patients, carers and physicians from medication-related issues, including adherence, to other important aspects of the patient's health and functioning, such as setting and attaining goals [19]. Whether such a shift in focus would also increase carer independence and confidence in their own future is an interesting question. In the current study, switching to PP3M reduced carer burden in the urging and worrying domains, which could suggest improvement in the QoL of carers, with more time and space to focus their attention elsewhere. In addition, although carer burden was relatively low in the supervision domain at baseline, a further reduction of burden in this domain may reflect the less frequent dosing (four times a year) required with PP3M compared with PP1M (12 times a year).

4.1. Limitations

The primary limitation of this study was that it was a single treatment arm, non-randomised, uncontrolled, open-label study, which did not allow for a direct head-to-head comparison of changes in carer burden for patients receiving PP3M versus PP1M. Furthermore, assessment of carer burden was an exploratory analysis and carer participation was not mandatory for this study. In total, 305 patients were enrolled and 291 completed the study [22]; 172 carers were identified, of whom 159 participated. The reasons for carers non-participation were not collected; some patients may not have had a participating carer because the study specifically excluded professional carers, and other patients may have decided not to include a carer. Therefore, it is unclear whether there are any important differences in the characteristics of carers who participated versus those who did not and whether this could have influenced the results, although we expect that this would have had minimal impact given the high participation rate (91%) of identified carers.

The study excluded patients with comorbid psychiatric disorders and severe substance use disorders, which can significantly impact carer burden; therefore, the study results may not be applicable to carers of patients with these conditions. Whilst patients with mild/moderate substance use disorders were eligible for inclusion, there were insufficient data to draw any conclusions on the impact of substance abuse on carer burden. There were also insufficient data for individual countries to be able to draw any conclusions regarding the impact of differing mental health systems and economic conditions among countries or regions from the results in this study. Finally, schizophrenia is a chronic disease, and therefore a 52-week study may

not provide a complete picture of carer burden; additional, longer term, real-world studies will be important to further understand the value of 3-monthly antipsychotic administration for carers.

5. Conclusions

In this naturalistic, clinical setting, switching patients with schizophrenia who were stable on PP1M to PP3M resulted in a reduction in carer burden, despite carers having only mild-to-moderate burden before the switch. At baseline, carer burden was greatest in the worrying and urging domains of the IEQ, which were improved at LOCF endpoint. Reductions in carer burden were observed across the different patient subgroups. These results demonstrate that switching stable patients with schizophrenia to a LAT that requires less frequent administration may benefit the carer as well as the patient. Longer term, real-world studies are warranted to expand on these findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2021.152233.

Previous presentation of data

Results from this study were presented in part at ECNP 2018; however, this particular sub-analysis was not included. Results of the REMISSIO study have been published in Garcia-Portilla M et al. *Therapeutic Advances in Psychopharmacology* 2020;10:1–20, but did not include this particular sub-analysis.

Data availability

The datasets used and/or analysed during the current study are available from the Yale University Open Data Access Initiative, at https://yoda.yale.edu/, reference number NCT02713282, on reasonable request, subject to possible IP, privacy, regulatory and/or other constraints.

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Declaration of Competing Interest

RL reports personal fees from Janssen Cilag and Otsuka, outside the submitted work. MGP reports grants and personal fees from Janssen-Cilag and Lundbeck; personal fees from Sage Therapeutics, Angelini, Otsuka and Pfizer, outside the submitted work. PB, SG, MM, AW and KP are employees of Janssen and are shareholders in the parent company (Johnson & Johnson).

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