Improving of Cognition and Quality of Life in Schizophrenia With One-month and Three-month Paliperidone Palmitate Treatment

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Abstract

An antipsychotic drug, Paliperidone palmitate (PDP), is administered to schizophrenics as injections at one-month (Sustenna) or three-month (Trinza) intervals. The present study was a series of clinical trial study, which included two sub-study, sought to compare the effects of treatment, social function, and side effects between two treatments in schizophrenics. In Study 1, total of 42 participants were received the Sustenna treatment for three months. In Study 2, total of 72 participants were recruited for Trinza treatment. The results showed Personal and Social Performance scales (PSP) significantly increased over time with both two treatments. Total cholesterol levels significantly decreased with Sustenna, which negatively influenced the cognitive functions, and the quality of life. UKU scales significantly decreased with Trinza after 15 months. In Brief, schizophrenics receiving PDP treatment presented improvements in their cognitive and social functions over the time, whether with the Sustenna or Trinza treatment. Total cholesterol and waist circumference decreased, and the LDL/HDL ratios increased over the time after PDP treatment. Furthermore, patients receiving Trinza treatment experienced decreased side effects. Nonetheless, schizophrenics had a significantly better quality of life after both Sustenna and Trinza treatment. Future studies should be consider larger samples and longer follow up.

Introduction

Schizophrenia is a chronic and severe psychiatric disorder. Affected patients experience positive symptoms, negative symptoms, and cognitive deficits, of which working memory problems are considered a central cognitive impairment.[1–5] Atypical antipsychotics are believed to have a superior effect in reducing both the positive and negative symptoms of schizophrenia, coupled with a low risk of extrapyramidal symptoms.[6] Particularly, 2nd -generation antipsychotic medications are commonly used in the treatment of schizophrenia.[7] Second-generation antipsychotics reduce the incidence and severity of side effects from 1st -generation antipsychotics, but 2nd -generation antipsychotics may induce cardiovascular and metabolic abnormalities (such as obesity, hyperglycemia, dyslipidemia, and the metabolic syndrome) that are associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease.[8–10]

In fact, one of major problems for patients with schizophrenia is their non-adherence to treatment. In fact, one of major problems for patients with schizophrenia is their non-adherence to treatment. As such, depot antipsychotics have been developed. Long-acting injections (LAIs) are administered only once every 2–4 weeks rather than each day to address the challenge presented by patient noncompliance.[10] Despite the intuitive assumptions that LAIs will yield superior compliance rates than oral antipsychotics for patients with schizophrenia, several studies have found no differences in compliance rates between oral and injected antipsychotics.[11,12] However, several studies have found that LAIs can lead to lower rates of noncompliance and re-hospitalization than oral antipsychotics.[13–15] Overall, previous studies have demonstrated that LAIs are as safe and effective a treatment in schizophrenia as oral antipsychotics, particularly 2nd -generation LAIs.[10–15]

Paliperidone palmitate (PDP) is delivered in the form of an LAI of the atypical antipsychotic paliperidone, the primary active metabolite of risperidone. Compared with other LAIs, PDP is able to more rapidly allow patients to reach and maintain a steady state over a longer period of time.[10] PDP's efficacy has been linked to its greater safety and tolerability, better cost–benefit ratio, lower withdrawal rate, lower relapse rates, and lower weight gain than other atypical antipsychotics.[16,17] Its pharmacokinetic characteristics are similar across ethnicities.[18] The standard dosing schedule is by induction therapy with a maintenance dose every 4 weeks (INVEGA SUSTENNA, once monthly injection) or 12 weeks (INVEGA TRINZA, once every 3 months injection). However, the differences between Sustenna and Trinza treatment remain unknown.

Hence, the aim of this study was to compare the treatment and side effects between Sustenna and Trinza protocols in patients with schizophrenia. Moreover, the changes in cognitive and lipid profiles between these two types of PDP were assessed. Furthermore, psychological functioning and performance, as well as quality of life, were assessed in this study.

Methods

Ethical statement

The present study was a series of clinical trial study, which included two sub-study. All procedures performed in the current study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board at Kaohsiung Armed Forces General Hospital (IRB-100046), and Joint Institutional Review Board at Taipei Veterans General Hospital (JIRB-08-013-P) in Taiwan. Also, this series of clinical trial study have registered in ClinicalTrials.gov (NCT03730857 in 05/11/2018 and NCT04754750 in 12/02/2021). After an explanation by senior psychiatrists, written informed consents were obtained either directly from the patients or from their legal guardians. All participants were notified that they could withdraw at anytime.

Study design

This series of clinical trial study, which included two sub-study, was a two and a half-one years, single-arm, nonrandomized, open-label study which was conducted between Jan 2015 and Jun 2017 based out of a psychiatric center in southern Taiwan.

- Study 1 (INVEGA SUSTENNA; PP1M study)

Stable schizophrenic patients who previously received risperidone by long-acting injection for more than one year were switched to a paliperidone palmitate treatment (INVEGA SUSTENNA, once monthly injection) after being included in the study. Participants were received the one-month long-acting injection (PP1M) for three months.

- Study 2 (INVEGA TRINZA; PP3M study)

Stable schizophrenic patients who previously received paliperidone palmitate by one-month long-acting injection for three month were switched to the three-month long-acting injection treatment (INVEGA TRINZA, once every 3 months injection; PP3M). Concomitant medications were allowed to prescribe except other antipsychotics.

Participants

In study 1 (PP1M study), total of 42 participants, including 25 men and 17 female, were received the one-month long-acting injection treatment for three months. In the study 2 (PP3M study), total of 72 participants, including 41men and 31 female, were recruited. Figure 1 presented the flow diagram of participants collecting process in PP1M and PP3M study. Patients who had comorbid serious medical illnesses, and may therefore present substantial clinical risk due to pharmacotherapy, were excluded from the sample, as were pregnant and lactating women. All of them had to meet the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[19]

Outcome measurements

Outcome measurements included the 20-item Toronto Alexithymia Scale (TAS-20), 45-item quality of life for mental disorder (QOLMD), Short-version of the Udvalg for Kliniske Undersogelser (short-version UKU), and Wisconsin Card Sorting test (WCST). These measurements were performed every three months except for the WCST, which was measured every six-months. The effect of treatment was assessed using Personal and Social Performance (PSP) scales[20,21] for the evaluation of psychosocial functioning at 0, 4, 8, and 12 weeks in the PP1M study, and at 0, 3, 6, 9, 12 months in the PP3M study, respectively. In addition, all participants were assessed for body weight, waist circumference, and their blood lipid profile. To assess the lipid profiles, fasting blood samples were analyzed for total cholesterol (TC), Triglyceride (TG), High-density Lipoprotein (HDL), and Low-density Lipoprotein (LDL) levels. These blood samples were collected at every month until study completion.

- 20-item Toronto Alexithymia Scale (TAS-20)

The traditional Chinese-language version of the 20-item TAS was validated in a Taiwanese student population by Lin and Chan.[22] The TAS scores were calculated for three sub-factors: 1) difficulty identifying feelings (DIF), 2) difficulty describing feelings (DDF), and 3) externally-oriented thinking (EOT). The 20 items are rated from 1 (strongly disagree) to 5 (strongly agree). The sum of all 20 items, considering reversed items, was used to generate a TAS total score. Those scoring greater or equal to 61 were considered alexithymic (high in alexithymia).[23]

- 45-item Quality of Life for Mental Disorders (QOLMD)

The QOLMD health survey measures HRQOL, and was revised based on the Quality of Life Interview Scale (QOLIS), which has 87 items and Quality of Life Scale (QLS),[24] which has 21 items. The QOLMD contains 45 items with eight dimensions, including 7 items on life satisfaction, 7 items on autonomy, 6 items on health maintenance, 5 items on family support, 5 items on economic ability, 7 items on social activities, 4 items on physical health, and 4 items on mental health, rated from 0 to 3. The internal consistency of the eight dimensions of the QOLMD revealed a Cronbach's alpha of .58-.84, and the corrected item-total correlations revealed a Pearson's $r > .30$.[25] A higher score represents a better health status.

- Short-version of the Udvalg for Kliniske Undersogelser (short-version UKU)

The nine items in the UKU-short were selected from those having high patient-doctor reliability (p less than 0.01),[26] with the addition of the four symptoms of somnolence, insomnia, dry mouth and dizziness, which were found to occur in the co-administration of antipsychotics,[27] and the deletion of the sexual dysfunction item. The selection process resulted in the two items on sedation and reduced sleep in the psychic side effect dimension, the four items on rigidity, tremor, akathisia and headache in the neurological side effects dimension, and the three items on reduced salivation, constipation and orthostatic dizziness in the autonomic side effects dimension. The procedure for using the short version is the same as that for the original UKU,[28] except that each item is defined by means of a 2-point-scale (0–1). In general, 0 means "not or doubtfully present", and 1 indicates that a symptom is present to a mild or severe degree. The Chinese version of the UKU presented good reliability and validity.[29]

- Wisconsin Card Sorting Test (WCST)

The computerized version of the WCST was developed based on the standardized criteria of Heaton, Chelune, Talley, Kay, & Curtiss[30] by Tien et al[31]. According to Heaton's criteria,[30] response results should be interpreted based on categories achieved, percent of perseverative errors and non-perseverative errors, percent of total errors, trials to complete the first category, conceptual level response, failure to maintain set, and learning-to-learn indices. The performance of cognitive function is to be assessed on the first week before receiving PDP treatment, as a baseline. Next, cognitive function is to be assessed at month 12 in the first, second, and after completed of the study.

Statistical Analysis

Data were analyzed using the SPSS 21.0 for Windows software package and subject to a demographic analysis and descriptive analysis. This study was based on a monotherapy design in two different antipsychotic treatments, and applied the Generalized Estimating Equations-I (GEE-I), developed by Liang and Zeger in 1986.[32]

AMOS for Windows 21.0 was used to apply a structural equation model (SEM) and to construct several theoretical models of the variables analyzed in this study. SEM uses the χ^2 fit test to assess the overall fit

of the hypothesized models; χ^2 values resulting in $p > 0.05$ and an adjusted goodness-of-fit index (AGFI) > 0.9 indicated that the model described the observed data adequately. The root mean square error of approximation (RMSEA) is based upon the non-centrality parameter. Good models using SEM supposedly have an RMSEA ≤ 0.05; however, models with an RMSEA of 0.10 or less are also acceptable.[33]

Results

Demographic data are listed in Table 1. After the generalized estimating equation analysis (GEE-I analysis), the results of the personal and social performance (PSP) scales demonstrated different effects of the two different long-acting injections of paliperidone palmitate (PP1M and PP3M) (Table 2). The results showed that the PSP scales were statistically significantly increasing over time in both PP1M (ß=3.438, p = 0.027) and PP3M (ß=0.969, p = 0.001) treatment protocols. In the PP1M treatment, the changes in PSP scales were related to the percent of conceptual level responses (ß=0.059, p = 0.001), waist circumference (ß=-0.143, p = 0.046), and sex (ß=-6.836, p = 0.001). In the PP3M treatment, the changes in the PSP scales were correlated to UKU scales (ß=1.262, p = 0.003) and LDL/HDL ratios (ß=0.197, p = 0.000).

Furthermore, the parsimonious structural equation models (SEM) confirmed the findings of the GEE-I analysis (Figs. 2 and 3). The results of these SEMs yielded *p* values greater than 0.05 (p = 0.543 and p = 130); the *p* values of the adjusted goodness-of-fit models were greater than 0.9 (AGFI = 0.954 and AGFI = 0.954), and yielded an RMSEA < 0.05 (RMSEA = 0.000 and RMSEA = 0.027). Hence, both of these two null models corresponded to the conceptual construct.

In Fig. 2, the results indicate that HbA1C statistically significantly increased with the PP1M treatment after 4 months (β = 0.18, p = 0.26), significantly negatively influencing waist circumference (ß=-0.19, p = 0.016), further positively influencing total cholesterol (ß=0.20, p = 0.10). However, total cholesterol statistically significantly decreased with the PP1M treatment (ß=-0.17, p = 0.026), negatively influencing the number of correct answers in the WCST (ß=-0.22, p = 0.005), and quality of life (ß=-0.23, p = 0.004). The PSP scales significantly increased with PP1M treatment after 4 months (ß=0.17, p = 0.017), further positively influencing quality of life (ß=0.20, p = 0.012). In addition, the number of correct answers in the WCST positively influenced the PSP scales (ß=0.35, p < 0.000).

In Fig. 3, UKU scales significant decreased with PP3M treatment after 15 months (ß=-0.15, p = 0.006). LDL/HDL ratios significantly negatively influenced the number of correct answers in the WCST (ß=-0.13, p = 0.012), negatively influencing interpersonal and social interactions (ß=-0.21, p < 0.000), further negatively influencing quality of life (ß=-0.22, p < 0.000). Older schizophrenic patients tended to have significantly negatively correlated to waist circumference (ß=-0.24, p < 0.000), drug dosage (ß=-0.31, p < 0.000), and number of correct answers in the WCST (ß=-0.27, p < 0.000), but positively correlated to interpersonal and social interaction (ß=0.16, p = 0.001). Males tended to have significantly negatively related to alexithymia scales (ß=-0.13, p = 0.008), further negatively influencing quality of life (ß=-0.28, p < 0.000), but positively influencing interpersonal and social interactions (ß=0.37, p < 0.000). Males also

had significantly negatively correlated to drug dosage (ß=-0.11, p = 0.021) and quality of life (ß=-0.13, p = 0.007). Age of onset was significantly positively related to drug dosage (ß=0.26, p < 0.000), and negatively correlated to the number of correct answers in the WCST (ß=-0.13, p = 0.016). The drug dosage significantly positively influenced interpersonal and social interactions (ß=0.14, p = 0.004), and negatively influenced quality of life (ß=-0.22, p < 0.000). In addition, there was a positive correlation between LDL/HDL ratio and waist circumference (r = 0.07). There was also a positive correlation between age and age at onset (r = 0.53), as well as age and sex (r = 0.10).

Discussion

Second-generation antipsychotics can attenuate the symptoms of schizophrenia, such as cognitive slowing, affective blunting, loss of spontaneity and volition.[34] As 2nd -generation LAI, PDP injections, including Sustenna (PP1M) and Trinza (PP3M), have been demonstrated to be effective in treatment maintenance in patients with schizophrenia.[10] However, the differences between PP1M and PP3M remain unknown. Hence, the current study sought to compare the effects of treatment and side effects between PP1M and PP3M. Moreover, changes in cognitive and lipid profiles, psychological function and performance, and quality of life were also assessed in this study.

In this study, results revealed that patients with schizophrenia experienced greater improvements in PSP total scores over time after receiving PP1M and PP3M. Particularly, the present study revealed that PP1M yields better improvements in the subdomains of disturbing and aggressive behaviors in PSP scores, while PP3M improved interpersonal and social interactions in patients with stable schizophrenia (data not shown). This means that whether patients received a PP1M or PP3M treatment would significantly improve total PSP scores (Table 2). Interestingly, both PP1M and PP3M improve PSP scores, although differentially so across different PSP subdomains.

Compared with PP3M, results showed an increase in the percentage of conceptual level responses in the WCST and a decrease in waist circumference in individuals receiving the PP1M treatment. Females tended to have higher PSP scores than males receiving PP1M (Table 2). Indeed, the higher waist circumference will increase total cholesterol, and further decrease cognitive function and quality of life. The structural equation model confirmed these findings (Fig. 2).

On the contrary, compared with PP1M, the findings also showed a decrease in UKU scores and increase in the LDL/HDL ratio in patients receiving PP3M treatment (Table 2). The further structural equation model also confirmed these findings (Fig. 3). That is, schizophrenics receiving the PP3M treatment will experience decreased side effects over the time. The LDL/HDL ratio, related to waist circumference, negatively influenced the number of correct answers in the patients receiving the PP3M. A higher LDL/HDL ratio will decrease cognitive function, and further influence interpersonal and social interactions, as well as patients' quality of life.

A previous study showed that a longer duration of untreated psychosis is associated poor social function in patients with schizophrenia.[35] The present study showed that an earlier onset of schizophrenia is associated with poor social function after a paliperidone palmitate dosage treatment, further decreasing patients' quality of life (Fig. 3). It is reasonable for chronic schizophrenia due to an earlier age of onset to be related to a longer duration of illness.

Previous studies showed that a drug with a lower or no 5-HT 2A affinity, such as quetiapine or amisulpride, is associated with a great improvement in cognitive function than a drug with a high affinity to 5-HT 2A receptors, such as risperidone, olanzapine, or clozapine.[36,37] However, these 5-HT 2A studies did not include the atypical antipsychotic paliperidone, which improves cognition and social functions.[38,39] The current study also confirmed the findings that both PP1M and PP3M improve cognitive and social function in patients with schizophrenia over time (Figs. 2 and 3).

In conclusion, patients with schizophrenia received paliperidone palmitate experienced improve cognitive and social function over the time, whether receiving a PP1M or PP3M treatment. Particularly, PP1M therapy yielded a significant improvement in the subdomains of disturbing and aggressive behaviors, and PP3M therapy yielded significant improvements in the evaluation of interpersonal and social interactions. Total cholesterol and waist circumference decreased, and the LDL/HDL ratio increased over time after paliperidone palmitate treatment. Furthermore, patients receiving a PPM3 therapy experience a decrease in side effects. Nonetheless, patients with schizophrenia have a great quality of life after both PP1M and PP3M therapy. These findings serve as a reference in clinical medicine. Future studies have to consider larger samples and longer follow up times.

Table 1
The demographic information of different Paliperidone palmitate treatment.

Paliperidone palmitate	times	N	Age	Sex	
				male	female
	1st time	42	47.38	25	17
PP1M	2nd time	42	47.36	25	17
(Sustenna)	3rd time	42	37.90	25	17
	4th time	30	51.57	14	16
	1st time	72	49.90	41	31
	2nd time	72	50.07	41	31
PP3M	3rd time	65	50.17	37	28
(Trinza)	4th time	63	50.65	36	27
	5th time	57	50.77	32	25

Table 2
Generalized estimating equation results for PSP scores related variables

Variable	ß	S.E.	Wald	p-value
PP1M (Sustenna)				
4th time	3.438	1.555	4.888	.027
3rd time	4.478	1.226	13.331	.000
2nd time	2.121	.750	8.012	.005
1st time	0			
Percent of conceptual level responses	.059	.018	10.468	.001
Waist circumference	− .143	.071	3.995	.046
sex	-6.836	2.114	10.458	.001
PP3M (Trinza)				
5th time	.969	.283	11.775	.001
4th time	.526	.283	3.462	.063
3rd time	.574	.252	5.188	.023
2nd time	.677	.280	5.867	.015
1st time	0			
UKU	1.262	.420	9.039	.003
LH	.197	.050	15.537	.000
DV: personal and social performance (PSP)				
UKU: the total scores of UKU				
LH: LDL/HDL ratio				

Abbreviations

PDP
Paliperidone palmitate
PP1M
one month long-acting injection
PP3M
three month long-acting injection
TAS-20
20-item Toronto Alexithymia Scale

QOLMD
45-itme quality of life for mental disorder
UKU
Udvalg for Kliniske Undersogelser scales
WCST
Wisconsin Card Sorting test
PSP
Personal and Social Performance scales
TC
total cholesterol
TG
Triglyceride
HDL
High-density Lipoprotein
LDL
Low-density Lipoprotein
GEE-I
Generalized Estimating Equations-I
SEM
structural equation model
AGFI
adjusted goodness-of-fit index
RMSEA
root mean square error of approximation
DSM-IV
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

Declarations

Conflict of Interest Statement

All authors have no conflict of interest to declare.

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Author contributions

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. CL and YC contributed to the data collection and analyses. CL and YC contributed to writing of the manuscript. P and FW supervised the execution and collection of

data, participated in the development of the protocol, performed the final data analyses, and edited the manuscript. All authors read and approved the final manuscript. No funder.

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Figures

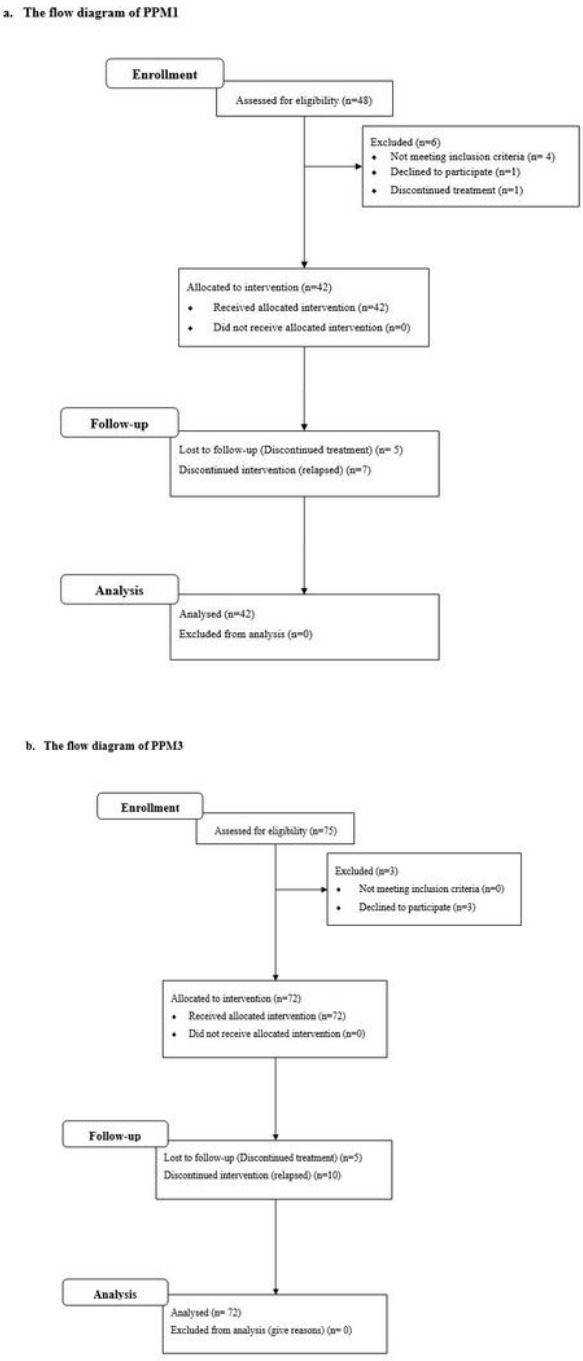

Figure 1

The flow diagram of participant collecting process

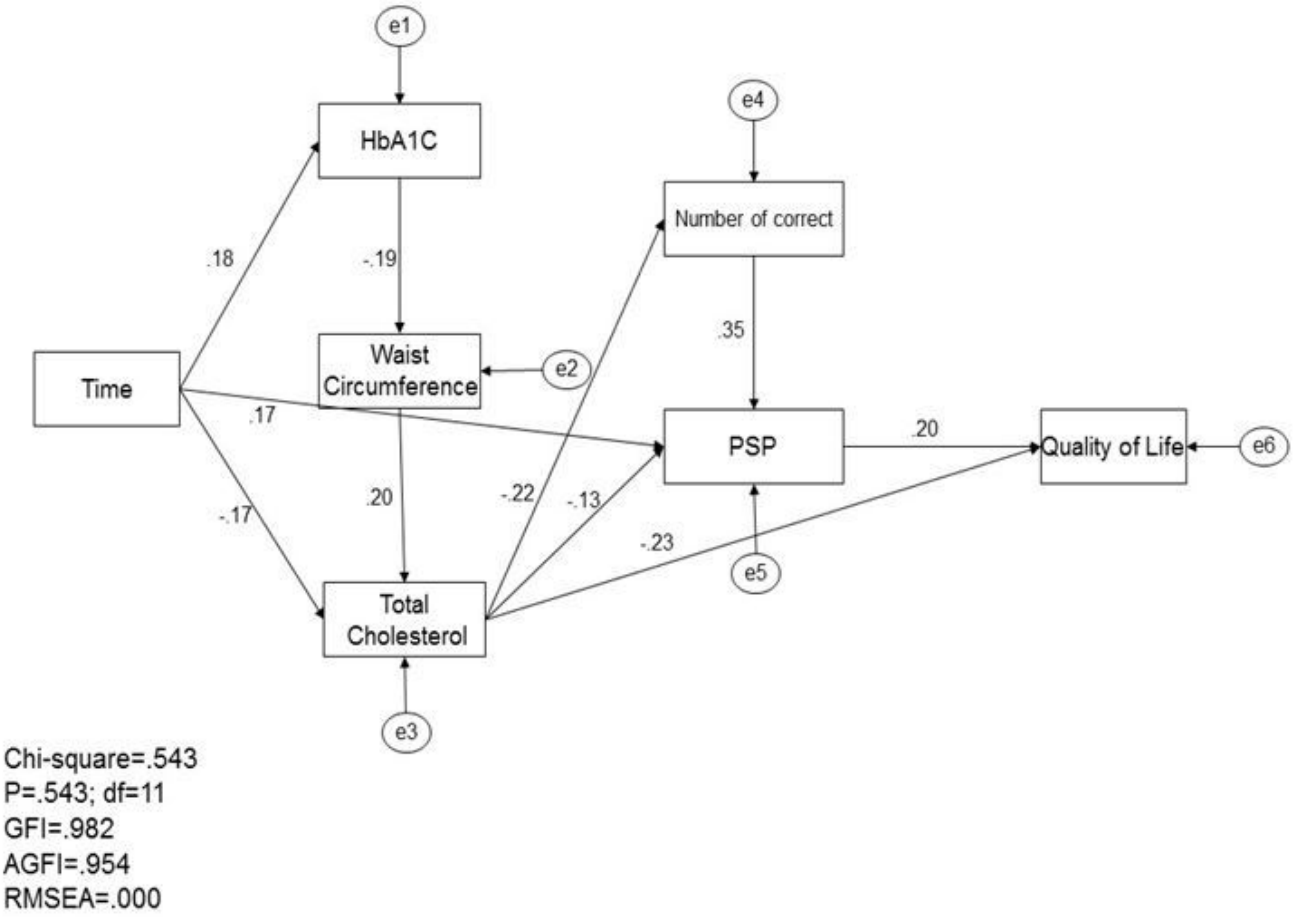

Figure 2

Parsimonious and conditional model of the associations between changes in PP3M of paliperidone (Trinza) extended-release

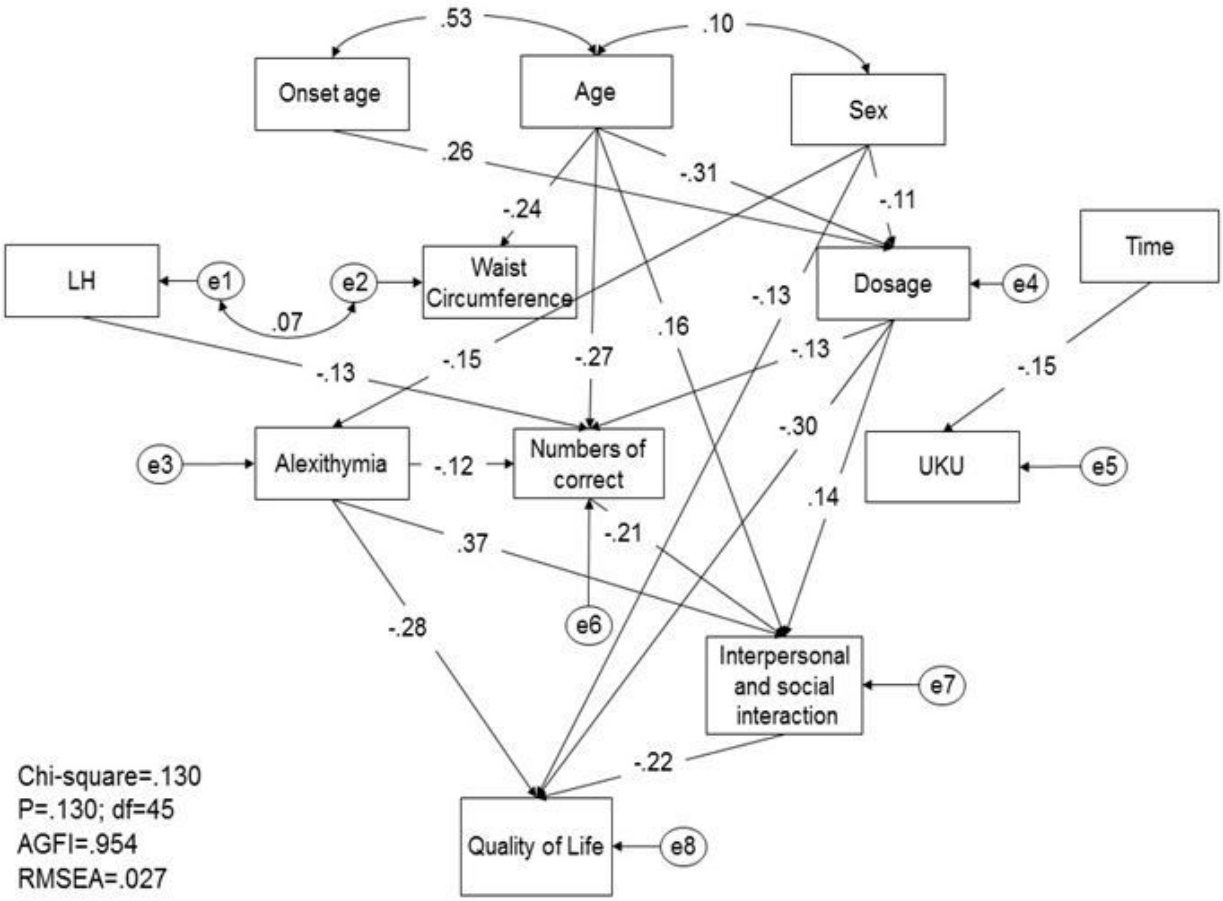

Figure 3

Parsimonious and conditional model of the associations between changes in PP3M of paliperidone (Trinza) extended-release

Supplementary Files

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- CONSORT2010Checklist.doc