treatment duration among 3 genotypes are listed in Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/JCP/A406. Table 1 also indicated that after adjustment for genetic factors, except for PANSS depressive factor score (P = 0.10), a higher dose of aripiprazole was associated with better improvement in PANSS positive, negative, excitement, and cognitive factor scores ($P < 0.0001$, < 0.0001, $= 0.0009$, and $= 0.0002$, respectively). Otherwise, longer duration of illness predicted poor improvement in the PANSS cognitive factor score on aripiprazole treatment ($P = 0.004$). When the effects of the *DRD2/ANKK1* Taq1A (rs1800497), *5-HT1A* C-1019G (rs6295), and *5-HT2A* T102C (rs6313) genetic variants together (Supplementary Table S3, Supplemental Digital Content 3, http://links.lww.com/JCP/A407) are taken into account, these modulate aripiprazole efficacy in different symptom dimensions of schizophrenia (DRD2/ANKK1 Taq1A [rs1800497] specifically for positive and excitement symptoms; 5-HT2A T102C [rs6313] specifically for negative symptoms; 5-HT1A C-1019G [rs6295] specifically for cognitive and depressive symptoms).

Aripiprazole acts as a partial agonist at 5-HT1A receptors, which is hypothesized to be associated with improvement of cognition and mood in schizophrenia.[10,11] The *C-1019G* genetic variant (rs6295) locates in the promoter region of the *5-HT1A* gene. It is functional in that the C allele is part of a 26-bp imperfect palindrome that binds NUDR protein to repress the *5-HT1A* gene, whereas the G allele abolishes repression by NUDR.[12] The C allele could bind NUDR to repress 5-HT1A densities, which seems to result in increasing the effect of aripiprazole. It is the possible reason why the C/C genotype of *5-HT1A C-1019G* (rs6295) genetic variant has better response to aripiprazole specifically for cognitive and depressive symptoms in our study.

Among aforementioned genetic findings, the result that the C/C genotype of *5-HT1A C-1019G* (rs6295) genetic variant has better response to aripiprazole specifically for cognitive and depressive symptoms is different to previous reports.[8] The 5-HT1A rs10042486-rs6295-rs1364043 T-G-T haplotype has been reported with better negative symptom improvement during treatment with perospirone or aripiprazole.[8] Conflicting results might have been due to the differences in assessment methods, subject's ethnicity, and nonethnic demographic factors. In addition, the fact that perospirone is somehow different from aripiprazole in pharmacological profile may also contribute to this discrepancy.

In addition to the aforementioned genetic factors, our results show that higher aripiprazole doses correlate with better treatment response in PANSS positive, negative, excitement, and cognitive factor scores. There is also a similar trait with depressive factor scores, but it is not statistically significant. Furthermore, increased duration of illness predicts inferior response for cognitive symptoms. This result supports the clinical finding that cognitive symptoms are more severe with increasing illness duration and often cause lower response to antipsychotic treatment.[13]

Combining with our previous research, the 3 genetic variants (*DRD2/ANKK1* Taq1A [rs1800497], *5-HT1A C-1019G* [rs6295], and *5-HT2A T102C* [rs6313]) could specifically predict aripiprazole efficacy in different symptom dimensions of schizophrenia. Confirmation in a larger sample should be required as well as in other racial and ethnic groups.

AUTHOR DISCLOSURE INFORMATION

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Shih-Fen Chen, PhD
Department of Molecular Biology and Human Genetics
Tzu Chi University
Hualien, Taiwan

Yu-Chih Shen, MD, PhD
Department of Psychiatry
Tzu Chi General Hospital at Hualien and School of Medicine
Tzu Chi University
Hualien, Taiwan
shengmp@gmail.com

REFERENCES

1. DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clin Ther*. 2004;26:649–666.
2. Uzun S, Kozumplik O, Mimica N, et al. Aripiprazole: an overview of a novel antipsychotic. *Psychiatr Danub*. 2005;17: 67–75.
3. Kwon JS, Kim E, Kang DH, et al. Taq1A polymorphism in the dopamine D2 receptor gene as a predictor of clinical response to aripiprazole. *Eur Neuropsychopharmacol*. 2008;18:897–907.
4. Shen YC, Chen SF, Chen CH, et al. Effects of DRD2/ANKK1 gene variations and clinical factors on aripiprazole efficacy in schizophrenic patients. *J Psychiatr Res*. 2009;43: 600–606.
5. Chen SF, Shen YC, Chen CH. Effects of the DRD3 Ser9Gly polymorphism on aripiprazole efficacy in schizophrenic patients as modified by clinical factors. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:470–474.
6. Miura I, Kanno-Nozaki K, Hino M, et al. Influence of -141C ins/del polymorphism in DRD2 gene on clinical symptoms and plasma homovanillic acid levels in the treatment of schizophrenia with aripiprazole. *J Clin Psychopharmacol*. 2015;35:333–334.
7. Chen SF, Shen YC, Chen CH. HTR2A A-1438G/T102C polymorphisms predict negative symptoms performance upon aripiprazole treatment in schizophrenic patients. *Psychopharmacology (Berl)*. 2009; 205:285–292.
8. Takekita Y, Fabbri C, Kato M, et al. HTR1A gene polymorphisms and 5-HT1A receptor partial agonist antipsychotics efficacy in schizophrenia. *J Clin Psychopharmacol*. 2015;35:220–227.
9. Wallwork RS, Fortgang R, Hashimoto R, et al. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. *Schizophr Res*. 2012;137: 246–250.
10. Newman-Tancredi A. The importance of 5-HT1A receptor agonism in antipsychotic drug action: rationale and perspectives. *Curr Opin Investig Drugs*. 2010;11: 802–812.
11. Schreiber R, Newman-Tancredi A. Improving cognition in schizophrenia with antipsychotics that elicit neurogenesis through 5-HT(1A) receptor activation. *Neurobiol Learn Mem*. 2014;110:72–80.
12. Lemonde S, Turecki G, Bakish D, et al. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J Neurosci*. 2003;23:8788–8799.
13. Lin CY, Tsai GE, Lane HY. Assessing and treating cognitive impairment in schizophrenia: current and future. *Curr Pharm Des*. 2014;20: 5127–5138.

Lavender Oil Preparation (Silexan) for Treating Anxiety
An Updated Meta-Analysis

To the Editors:

Anxiety disorders are the most prevalent mental health conditions. Despite robust and effective pharmacological and therapeutic approaches, approximately 25% of patients respond poorly to treatment and show a high risk of chronicity. As a result, anxiety disorders can be said to account for decreased productivity, increased morbidity and mortality rates, and the growth of alcohol

and drug abuse in a large segment of the population.[1] In this scenario, new treatment options are constantly under investigation.

Silexan (lavender oil) has been modernly used for treatment of disruptive anxiety. Lavender *(Lavandula angustifolia)* has been known for centuries as a medicinal plant. It has been ascribed anxiolytic as well as calming properties and as such it is justified to investigate the efficacy of this herbal drug as an anxiolytic agent. As an oil derived from the flowers of the plant by steam distillation, the herbal essence is a complex, multiingredient mixture in which more than 160 different substances have been identified. The anxiolytic properties of the drug have been ascribed to different ingredients. According to in vitro studies, lavender oil exerts effects on the $GABA_A$ receptor and inhibits the presynaptic calcium channels.[2]

Recent publications have been underscoring clinical benefits of Silexan over subsyndromal anxiety, generalized anxiety disorder, mixed anxiety and depressive disorder, and anxiety-related restlessness with favorable results. We report on a systematic review and meta-analysis of all available up-to-date controlled trials of clinical studies assessing the effects of Silexan over anxiety after the recommendations of the Cochrane group.[3] All analyses were performed using the statistical packages for meta-analysis of *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP. for Mac OSX. For the main outcome (anxiety symptoms), we initially calculated the standardized mean difference and the pooled standard deviation of each comparison. The Hedges g was used as the measure of effect size, which is appropriate for studies of small sample sizes. The pooled effect size was weighted by the inverse variance method and measured using the random-effects model. Heterogeneity was evaluated with the I^2 (>35% for heterogeneity) and the χ^2 test ($P < 0.10$ for heterogeneity). Publication bias was evaluated using the Egger regression intercept test and the funnel plot, which displays confidence interval boundaries to assist in visualizing whether the studies are within the funnel, thus providing an estimate of publication bias (eg, whether the studies are distributed asymmetrically and/or fall outside the funnel). Sensitivity analysis, which assesses the impact of each study in the overall results by excluding 1 study at a time, was also performed.

Five studies (n = 1165) were included in the meta-analysis.[4–8] One study was imputed twice[6] given the authors assessed 2 different Silexan dosages in comparison with placebo. Patients presented a mean age of 46.9 ± 1.2 years. Two studies included patients diagnosed with generalized anxiety disorder,[6,8] one study evaluated patients with mixed-anxiety depression,[4] 1 trial assessed patients with anxiety-related restlessness,[5] and 1 trial assessed patients with subsyndromal anxiety.[7] All but 1 study compared Silexan (80 or 160 mg) with placebo. One study used an active comparator group (lorazepam) and was included in the final analysis to guarantee a more conservative analysis.[8]

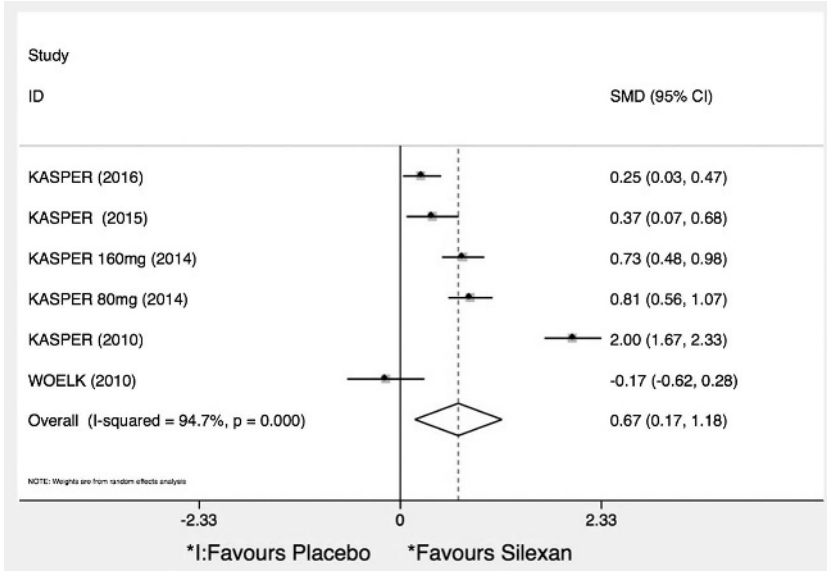

FIGURE 1. Forest plot of effect sizes (Hedges g) for active versus placebo group. CI, Confidence interval.

We found Silexan to be significantly superior to placebo in ameliorating anxiety symptoms independently of diagnosis (Hedges g = 0.67; 95% confidence interval [CI], 0.16–1.67) (Fig. 1). Interestingly, there was a tendency for greater clinical effect when analyzing separately generalized anxiety disorder patients in comparison with all other diagnosis (Hedges g = 0.50; 95% CI, 0.02–0.97 vs Hedges g = 0.87; 95% CI, −0.16–1.90). In addition, we found Silexan to be superior to placebo and as effective as active comparator group (lorazepam) in the pooled analysis.

Primary outcome was based on amelioration of anxiety symptoms, assessed continuously by the Hamilton Anxiety Scale. Heterogeneity was, however, substantial in our analysis ($I^2 > 35\%$ and $P < 0.0001$ for the χ^2 test) underscoring the need for further standardization among studies regarding both eligibility criteria to determine more homogenous samples and experimental protocols. The other study limitation was the small number of studies, which may also compromise external validity. Regarding each study individually, we ought to underscore the lack of blinding assessment, the small samples, and the heterogeneity regarding eligibility criteria as main limitations to our final analysis.

Our results point toward a positive association between Silexan and amelioration of anxiety symptoms mainly regarding generalized anxiety disorder patients. Notwithstanding, given the relatively small number of trials published to date, further trials with greater sample sizes and more standardized experimental protocols will aid to clarify the precise effects of this promising therapeutic tool in clinical psychiatry.

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The present work was performed at the Interdisciplinary Center for Clinical Neuromodulation, Santa Casa School of Medical Sciences, São Paulo, Brazil.

Marcelo B. Generoso, MD
Amanda Soares, MSc
Ivan T. Taiar, MSc
Quirino Cordeiro, MD, PhD
Clinical Neuromodulation Laboratory – Santa Casa School of Medicine
São Paulo, Brazil

Pedro Shiozawa, MD
Clinical Neuromodulation Laboratory – Santa Casa School of Medicine
São Paulo, Brazil
pedroshiozawa@gmail.com

REFERENCES

1. Bystritsky A, Khalsa SS, Cameron ME, et al. Current diagnosis and treatment of anxiety disorders. *PT*. 2013;38:30–57.
2. de Groot AC, Schmidt E. Essential Oils, Part I: Introduction. *Dermatitis*. 2016;27:39–42.
3. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009; 6:e1000100.
4. Kasper S, Volz HP, Dienel A, et al. Efficacy of Silexan in mixed anxiety-depression—a randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2016;26:331–340.
5. Kasper S, Anghelescu I, Dienel A. Efficacy of orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep—a randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2015;25:1960–1967.
6. Kasper S, Gastpar M, Müller WE, et al. Lavender oil preparation Silexan is effective in generalized anxiety disorder—a randomized, double-blind comparison to placebo and paroxetine. *Int J Neuropsychopharmacol*. 2014; 17:859–869.
7. Kasper S, Gastpar M, Müller WE, et al. Silexan, an orally administered Lavandula oil preparation, is effective in the treatment of 'subsyndromal' anxiety disorder: a randomized, double-blind, placebo controlled trial. *Int Clin Psychopharmacol*. 2010;25:277–287.
8. Woelk H, Schläfke S. A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. *Phytomedicine*. 2010;17:94–99.

Memantine Plasma Concentrations Among Patients With Dementia

To the Editors:

Memantine (Namenda) was approved in the United States by the Food and Drug Administration in October 2003 for the treatment of moderate to severe Alzheimer dementia. Tablets are currently available in the United States in 5- and 10-mg standard release formulations and are administered in doses ranging from 5 mg daily to more typically 10 mg twice daily. A once-daily (XR) preparation was released in mid-2013. This once-daily formulation is available in 7-, 14-, 21-, and 28-mg doses.

In February 2014, the manufacturer reported that sales of the standard release formulation in the United States would cease on August 15, 2014, and clinicians would be required to maintain treatment with the XR formulation.

In anticipation of this so-called "forced switch," we recruited subjects for the purposes of analyzing changes in plasma memantine concentrations as a result of this switch from a typical dose of 10 mg twice daily to 28 mg once daily. After institutional review board approval, 19 subjects were recruited for the study. After the first blood draw, the Attorney General of New York successfully blocked the manufacturer from discontinuing the production of standard tablets. The study was therefore halted because patients were no longer forced to switch to the once-daily formulation, and therefore, the second blood draw was not obtained.

We report the steady state plasma concentrations of memantine among elderly patients with dementia chronically treated with standard tablets.

After institutional review board approval, consent was obtained from the legally authorized patient representative, and patients were recruited from both the outpatient practice of the Division of Geriatric Medicine and a local affiliated nursing home. Trough blood level for plasma memantine assay was obtained before the first dose of the day, as well as demographic information among patients chronically treated with this drug. Serum was also analyzed for blood urea nitrogen, albumin, and creatinine. These latter analytes were obtained to estimate renal function using both the Cockcroft-Gault[1] and Modification of Diet in Renal Disease (MDRD)[2] formulas. For patients with serum creatinine levels less than 1.0 mg/dL, we rounded the value to 1. Plasma memantine was assayed using high-pressure liquid chromatography combined with mass spectrometry. Pearson correlation coefficients were used to describe the association between plasma memantine concentration per unit daily dose and renal function. Scatter plots were generated and presented along with estimated regression lines to characterize associations.

The 19 patients studied had a mean age of 87.6 years (range, 76–101 y); 12 were men, and 7 were women. Twelve of the 19 patients were treated with memantine 10 mg twice daily, 5 patients received a total daily dose of 10 mg, and 2 patients received a total daily dose of 15 mg. All 10 nursing home patients were treated with 10 mg twice daily. Renal function was calculated to be a mean (SD) of 42.4 (14.0) (range, 24.5–75.4) and 55.2 (8.6) (range, 41.5–69.9)mL/min by the Cockcroft-Gault and MDRD methods, respectively. The mean (SD) plasma memantine concentrations adjusted for total daily dose was 15.5 (9.5)ng/mL/mg of memantine (range, 3.9–41.0 ng/mL/mg); that is, typical concentrations for a patient receiving 20 mg daily would be 310 ng/mL but with large interindividual variability (range, 78–820 ng/mL).

The correlation between plasma memantine concentrations and renal function was not significant: adjusted MDRD formula, −0.41 (R^2 = 0.17, P = 0.08); adjusted Cockcroft- Gault equation, −0.27 (R^2 = 0.07, P = 0.27). The relationship between adjusted MDRD calculated renal function and dose-adjusted plasma level is illustrated in Figure 1.

To our knowledge, plasma concentrations of memantine among elderly people with dementia receiving this agent chronically have not been published. Single-dose pharmacokinetic studies of memantine have been performed,[3,4] but we are not aware of any studies among chronically treated elderly patients with Alzheimer dementia. One study reported on pharmacokinetics among a diverse group of patients aged 18 to 99 years receiving memantine for various indications but without reference to renal function.[5] Although not reaching a level of statistical significance, the results of our study are not necessarily inconsistent with first-order pharmacokinetics related to a renal clearance mechanism for this drug. Strong correlations with renal function may not necessarily be expected because the drug also undergoes hepatic metabolism.[3,6] Our results also demonstrate that factors besides renal function are important determinants of plasma concentration because the variance in levels attributable to renal function is small even when measured by the MDRD formula (R^2 = 0.17; Fig. 1). Dosing recommendations, however, are based on kinetic studies that showed a dependence on renal clearance for total drug clearance.[3] This study was originally powered to show the before-and-after effect of switching dosing formulations, but the current study is informative because plasma levels have not previously been reported among elderly patients with dementia on chronic therapy. In fact, the mean levels in this study are 2 to 3 fold higher than those that would have been predicted based on the single-dose studies,[3,4] including subjects with similar impairments in renal function[3] and as predicted on the