Main body: 3097 words

Number of references: 40

Tables: 4

Figure: 0

Supplementary eTables: 3

Abstract: 249 words

(Regular Research Article)

Lack of early improvement with antipsychotics is a marker for subsequent non-response in behavioral and psychological symptoms of dementia: Analysis of CATIE-AD data

Abbreviated title: Lack of Early Improvement in Dementia

Kazunari Yoshida, MD[a], Rachel Roberts, MS[b], Takefumi Suzuki, MD, PhD[a, c], Barry Lebowitz, PhD[d], Suzanne Reeves, PhD[e, f], Robert Howard MD[e, f], Takayuki Abe, PhD[b], Masaru Mimura MD, PhD[a], Hiroyuki Uchida, MD, PhD[a, g]

[a.] Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

[b.] Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan

[c.] Department of Psychiatry, Inokashira Hospital, Tokyo, Japan

[d.] Department of Psychiatry, University of California, San Diego, CA, USA

[e.] Division of Psychiatry, University College London, London, UK

[f.] Department of Old Age Psychiatry, Institute of Psychiatry, King's College London,

London, UK

[g.] Geriatric Psychiatry Division, Centre for Addiction and Mental Health, Toronto, ON, Canada

Corresponding author:

Hiroyuki Uchida, MD, PhD

Department of Neuropsychiatry, Keio University School of Medicine

35, Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan.

email: hiroyuki.uchida.hu@gmail.com

Phone: +81.3.5363.3829

Fax: +81.3.5379.0187

Funding/Support:

Data used in the preparation of this article were obtained from the limited access datasets distributed from the Clinical Antipsychotic Trials in Intervention Effectiveness with Alzheimer's Disease (CATIE-AD). This is a multisite, clinical trial of persons with Alzheimer's Disease, comparing the effectiveness of randomly assigned medication treatment. The study was supported by NIMH Contract #N01MH90001 and by U.S. Department of Veterans Affairs. Medications for this study were provided by

AstraZeneca Pharmaceuticals, Forest Pharmaceuticals, Janssen Pharmaceutica, and Eli Lilly. The ClinicalTrials.gov identifier is NCT00015548. The version of the dataset used was 1.0. This manuscript reflects the views of the authors and may not reflect the opinions or views of the CATIE-AD Study Investigators or the NIH. No funding was provided for the present analysis.

Previous presentation:

1. Poster presentation: American Society of Clinical Psychopharmacology, Miami, 2015. 6. 24.
2. Oral presentation: 25th Congress of the Japanese Society of Clinical Neuropsychopharmacology, Tokyo, 2015. 10. 30.
3. Poster presentation: 4th Congress of Asian College of Neuropsychopharmacology, Taipei, 2015. 11. 20.
4. Poster presentation: 30th Collegium Internationale Neuro-Psychopharmacologium, Seoul, 2016. 7. 5.

Acknowledgments:

None

Potential Conflicts of Interest:

Dr. Yoshida has received manuscript fees or speaker's honoraria from Meiji Seika Pharma, Sumitomo Dainippon Pharma, and Eli Lilly and consultant fees from Bracket within the past three years. Dr. Suzuki has received manuscript or speaker's honoraria from Astellas, Sumitomo Dainippon Pharma, Eli Lilly, Elsevier Japan, Janssen Pharmaceuticals, Meiji Seika Pharma, Novartis, Otsuka Pharmaceutical, and Wiley Japan within the past three years. Dr. Abe has received speaker's honoraria from Boehringer Ingelheim within the past three years. Dr. Mimura has received grants and/or speaker's honoraria from Asahi Kasei Pharma, Astellas, Daiichi Sankyo, Sumitomo Dainippon Pharma, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceuticals, Meiji Seika Pharma, Mochida Pharmaceutical, MSD, Novartis, Otsuka Pharmaceutical, Pfizer, Tsumura, Shionogi, Takeda, Tanabe Mitsubishi Pharma, and Yoshitomi Yakuhin within the past three years. Dr. Uchida has received grants from Astellas, Eisai, Otsuka Pharmaceutical, GlaxoSmithKline, Shionogi, Sumitomo Dainippon Pharma, Eli Lilly, Mochida Pharmaceutical, Meiji Seika Pharma, and Yoshitomi Yakuhin and speaker's honoraria from Otsuka Pharmaceutical, Eli Lilly, Shionogi, GlaxoSmithKline, Yoshitomi Yakuhin,

Sumitomo Dainippon Pharma, Meiji Seika Pharma, Abbvie, MSD, and Janssen Pharmaceuticals within the past three years. Other authors have nothing to disclose.

ABSTRACT

Objective: Prediction of response/non-response to antipsychotics is especially important in patients with behavioral and psychological symptoms of dementia (BPSD) in whom antipsychotic exposure increases risks of death. We aimed to examine whether presence/absence of early improvement of BPSD with antipsychotics is associated with subsequent response/non-response.

Design: Post-hoc analysis of the Clinical Antipsychotic Trials in Intervention Effectiveness with Alzheimer's Disease (CATIE-AD) study (2001-2004) (trial registration: NCT00015548).

Setting: 45 sites in the United States.

Participants: 245 subjects (olanzapine, n=90; quetiapine, n=81; risperidone, n=74) with a DSM-IV diagnosis of dementia of the Alzheimer's type who presented with a score of 1 or more in the Brief Psychiatric Rating Scale (BPRS) at baseline (Phase 1 of CATIE-AD).

Intervention: Subjects were randomly assigned to treatment with olanzapine, quetiapine, risperidone, or placebo in a double-blind manner.

Measurements: We examined associations between response at week 8, and demographic and clinical characteristics, including BPRS total score reduction at week 2, using logistic regression analyses. Prediction performance of binary classification (presence/absence) of improvement/no improvement at week 2 for response at week 8 was examined.

Results: BPRS total score reduction at week 2 (mean percentage score reduction, 12.6%) was significantly associated with response at week 8 (odds ratio, 1.18; 95% CI, 1.11-1.26). The 5% score reduction cut-off at week 2 showed the highest accuracy (0.71) with sensitivity, specificity, PPV, and NPV of 0.76, 0.65, 0.69, and 0.72, respectively.

Conclusion: Lack of even a very small early improvement with antipsychotic treatment may be a marker of subsequent non-response in BPSD.

Keywords:

antipsychotics, behavioral and psychological symptoms with dementia (BPSD), CATIE-AD, dementia, prediction, response

Introduction

Behavioral and psychological symptoms such as delusions, hallucinations, agitation and aggression are difficult to manage in patients with dementia.[1] While non-psychopharmacological interventions are the first option to consider, drug treatments are widely used.[2,3] Antipsychotic drugs have the best evidence for effectiveness in the management of behavioral and psychological symptoms with dementia (BPSD).[4] However, use of antipsychotic medication continues to be controversial and subject to scrutiny and international policy oversight, as substantial morbidity and increased mortality associated with their use[5,6] led to a US Food and Drug Administration (FDA) black box warning against the use of atypical antipsychotics in patients with dementia.[7,8] More recently, a 2014 update to the American Psychiatric Association's Practice Guidelines recommends that antipsychotics must be used with caution and at the lowest effective dosage because they are associated with severe adverse events.[9] Further, the frequency, severity and potential consequences of the adverse effects of antipsychotics are greater in older patients due to age-related changes in pharmacokinetic and

pharmacodynamics parameters.[10,11] Therefore, it would be clinically important to identify potential responders and non-responders to antipsychotic treatment as early as possible after treatment is initiated to inform benefit-risk considerations in individual patients.[12,13] If such response prediction is valid, those who are unlikely to respond to a particular drug could be switched to another treatment option, hence reducing exposure to antipsychotics that offer little clinical gain.[12-14]

In patients with schizophrenia, a number of previous studies have shown that early improvement following antipsychotic drug use is associated with subsequent favorable treatment outcomes.[12,13,15] Likewise, lack of early improvement with antipsychotics predicts unfavorable outcomes at endpoint and this has already been incorporated into treatment guidelines.[16] The same holds for treatment of depression with antidepressants.[14,17] However, no studies have investigated the ability of early symptom improvement to predict later response with antipsychotics in patients with BPSD.

To investigate this, we conducted a post-hoc analysis of the data from the Clinical

Antipsychotic Trial of Intervention Effectiveness-Alzheimer's disease (CATIE-AD)[18,19] to examine whether presence/absence of improvement with antipsychotics (olanzapine, quetiapine, and risperidone) after 2 weeks treatment would be associated with treatment response/non-response at week 8 in patients with BPSD.

Methods

Study design

The CATIE-AD was funded by the National Institute of Mental Health to compare the effectiveness of antipsychotic drugs in patients with Alzheimer's disease and psychosis or agitated/aggressive behavior. The study has been described in detail elsewhere.[18,19] Briefly, it was conducted between April 2001 and November 2004 at 45 clinical sites in the United States. Four hundred and twenty-one patients with a diagnosis of dementia of the Alzheimer's type based on the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)[20] or probable Alzheimer's disease based on the National Institute of Neurological and Communicative Disorders Association (NINCDA-ADRDA),[21] participated in the trial. Patients were initially randomized to olanzapine, quetiapine, risperidone, or placebo under double-blind conditions, and received treatment for up to 36 weeks or until treatment was discontinued for any reason (Phase 1). Medications were prepared in low-dose and high-dose capsules (olanzapine: 2.5 mg or 5.0 mg, quetiapine: 25 mg or 50 mg and risperidone: 0.5 mg or

1.0 mg, respectively). Study physicians adjusted medication dosage based on their clinical judgment and patient response.

Data used in this analysis were derived from the patients who were receiving olanzapine, quetiapine, or risperidone and received assessments with the Brief Psychiatric Rating Scale (BPRS)[22] or the Neuropsychiatric Inventory (NPI)[23] at both baseline and week 2 in Phase 1 of CATIE-AD. The protocols were approved by the local institutional review boards, and all patients gave written informed consent to participate in this trial. Ethical approval was not sought for this specific analysis that used completely anonymous data.

Clinical Subtypes

Based on the data in Phase 1 of CATIE-AD, patients were classified by age group (i.e. ages of ≤69 years or ≥70), sex, race (i.e. white vs. other), and dementia psychosis subtype (i.e. paranoid, misidentification, mixed, and non-psychotic). This categorization was based on factorial analysis of NPI delusions and hallucinations domains,[24,25] which identified two factors: a 'paranoid' subtype (delusions of persecution and/or

abandonment); and a ‘misidentification’ subtype (misidentification phenomena and/or hallucinations). Patients who were experiencing both types of symptoms were described as ‘mixed’.

Statistical analysis

First, to examine factors associated with response at week 8, binary logistic regression analyses were conducted with antipsychotic medication used, gender, age group, race, dementia psychosis subtype (only for NPI analysis), total score in the BPRS or NPI at baseline, and reduction in the BPRS or NPI total scores from baseline to week 2. A multivariate model was used for the last 2 variables (i.e. total score in the BPRS or NPI at baseline, and reduction in the BPRS or NPI total scores from baseline to week 2) and univariate model for the other variables. With regard to the definition of response, a score reduction of ≥one minimal clinically important difference (MCID),[26,27] defined as a half of the standard deviation (SD) of change from baseline at week 8 in the BPRS or NPI was adopted; MCIDs were 6.4 to 7.6 for BPRS and 8.3 to 10.5 for NPI, depending on the dataset generated with multiple imputations[28] as described below.

Next, the prediction performance of binary classification of early improvement at week 2 (present or absent) for response at week 8 was examined. To this end, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the consecutive cut-off points in 5% increments between 5% and 25% in the BPRS total or NPI total scores at week 2 were calculated. To seek the optimum cut-off point, accuracy, defined as (True Positive + True Negative) / Total N, was calculated. Accuracy depends on the number of observations, which may render it inferior to the careful and balanced consideration of sensitivity and specificity. To address this potential pitfall, cut-off points that demonstrated a level of ≥0.5 in both sensitivity and specificity with the highest degree of accuracy were examined.[29] In addition, the area under the curve (AUC) of the receiver operating characteristic (ROC) was also calculated.

Multiple imputation of the outcome and predictors was performed to deal with missing values, using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA.). To account for variability in imputed values, 100 imputed data sets were created using Proc MI (a

procedure within SAS) using Markov chain Monte Carlo (MCMC) imputation method. Multiple imputation is a method in which missing values are replaced with predicted values from a regression model, but in order to reincorporate variance that is lost by using a simple prediction, a residual term is added to each value based on a normal distribution with mean zero and variance equal to the residual variance from the regression model. In the case of this study the imputation was single-chain done with 200 burn-in iterations, as are the default settings. The imputation was done 100 times (as mentioned above), the resulting datasets were then analyzed and the results were pooled using Proc MIANALYZE. Other statistical analyses, including additional available case analysis, were performed, using SPSS version 22.0 (IBM, New York). A p-value of <0.05 was considered statistically significant (two-tailed).

Results

Subject characteristics

All two-hundred forty-five patients (olanzapine, n=90; quetiapine, n=81; risperidone, n=74) and 242 patients (olanzapine, n=90; quetiapine, n=80; risperidone, n=72) in the intention-to-treat (ITT) samples were included in the analyses for the BPRS and NPI, respectively. Demographic and clinical characteristics are summarized in Table 1.

Insert Table 1 Here

Factors associated with response to antipsychotic drugs at week 8

The missing proportions (out of 245) for the variables included in the BPRS imputation model were 28.9%, 52.2%, and 62% respectively for the variable BPRS at weeks 4, 8, and 12. Baseline BPRS values and week 2 values were complete. The missing proportions

(out of 242) for the variables included in the NPI imputation model were 28.1%, 51.6%, and 61.5% respectively for the variable NPI at weeks 4, 8, and 12. Baseline NPI values and week 2 values were complete. There were no missing values for other variables (i.e. age, sex, race, antipsychotics, or subtype). The total score reduction in the BPRS or NPI at week 2 was significantly associated with subsequent response to antipsychotic treatment at week 8 (Tables 2 and 3). In contrast, factors other than the total score in the BPRS or NPI at baseline failed to show any association with subsequent response. Results obtained with an available case analysis were similar to these findings (Supplementary Tables 1 and 2).

Insert Tables 2 and 3 Here

Prediction performance of presence/absence of improvement at week 2 for response at week 8

The prediction performance of binary classification of early improvement at week 2 for response at week 8 is shown in Table 4; sensitivity and NPV were slightly higher than specificity and PPV. The 5% cut-offs in the BPRS and the NPI at week 2 showed the highest degree of accuracy for the prediction of response at week 8. The ROC analysis demonstrated high values for the use of BPRS and NPI total score reductions for the prediction of response at week 8 with 0.76 and 0.75, respectively. The 5% and 10% cut-offs in BPRS and NPI at week 2 showed the highest degree of accuracy for the prediction of response at week 8, respectively, when available case analysis was employed (Supplementary Table 3).

Insert Table 4 Here

Discussion

As the proportion of aging individuals within society increases, the management of BPSD represents an urgent unresolved clinical issue. To our knowledge, this is the first study to investigate the impact of presence/absence of early improvement with antipsychotic drugs on subsequent treatment outcomes in patients with BPSD. We found that the reduction in total score at week 2 was significantly associated with subsequent clinically important response at week 8 although the modest magnitude of the association should be taken into account. Furthermore, score reductions of 5% in the BPRS and NPI total scores at week 2 appeared to perform well as clinically relevant cut-offs, with the highest degree of accuracy for the prediction of response at week 8. Given the fact that NPVs were higher than PPVs, these findings suggest that, if there is no improvement in the early stage of treatment, continuation of the antipsychotic in question is likely to be futile.

Previous studies focusing on patients with schizophrenia or major depressive disorders (MDD) have shown that presence/absence of early improvement with antipsychotics or

antidepressants can be a robust predictor of subsequent response/non-response[12,13,15,17,30-32] although the conditions of psychosis and mood symptoms may substantially differ among patients with schizophrenia, MDD, and AD. In patients with schizophrenia, improvements such as a ≥25% reduction in the BPRS or a ≥20% reduction in the Positive and Negative Syndrome Scale (PANSS)[33] total score at week 2 predict response at 4, 8, and 12 weeks, while lack of such initial improvement at week 2 is associated with poor outcomes thereafter.[12,15,30] Such associations have also been previously identified in relation to antidepressant treatment.[17,31,32] Since there has been no prior report of the degree of change that should be used to define early improvement with antipsychotic treatment in BPSD, we tested consecutive cut-off points to explore the optimum threshold. In contrast to those previous studies, optimally performing cut-offs were relatively low (5% for BPRS and NPI, respectively) in the current study. This discrepancy is likely attributable to differences in symptom trajectories over time in people with dementia compared to other illnesses and the heterogeneous nature of symptoms contained within the nonspecific treatment target that BPSD represents. In the present study, the mean percentage score reduction in the BPRS total score at week 2 was as low as 12.6% (from

27.0 to 23.6), for which floor effects should be taken into account. This reduction is much lower than seen in schizophrenia trials. For example, one double-blind randomized controlled trial data of schizophrenia patients demonstrated that the mean percentage score reduction in the PANSS at week 2 was 29.2% (from 95.0 to 67.3) for risperidone and 21.1% (from 97.3 to 76.8) for quetiapine,[34] which roughly corresponds to a percentage BPRS improvement of 30%.[35] Thus, the symptom improvement from baseline to week 2 reported in schizophrenia seems greater than that in BPSD with modest severity. These low cut-off values (i.e. 5%), with high NPVs, seen in our study reinforce the observation that patients with no improvement at the early stage of antipsychotic treatment in BPSD are unlikely to derive any further clinical benefit thereafter. Prediction of non-response is especially important in patients with BPSD in whom the exposure to antipsychotic drugs has been reported to increase risks of serious side effects, including death.[7,36] Those potential non-responders may benefit from a switch from antipsychotic treatment that will unlikely work to another treatment option at the earliest opportunity; this will also minimize the exposure to antipsychotic drugs and hence reduce such lethal adverse events.

Prediction performance in the present study was high and comparable to that in previous studies that have included patients with schizophrenia; for example, lack of early improvement at 2 weeks predicted subsequent non-response at week 8 or 12 with NPVs of 0.73-0.84.[12,15] Thus, early improvement with antipsychotic treatment could serve as a robust predictor of subsequent treatment response, irrespective of diagnoses. While the prediction performance in the present study seems high, it should be noted that 20-30% of the patients were still judged as false positives or false negatives. Therefore, further investigations are clearly needed to improve the prediction performance to reduce the risk of misclassifications.

The association between lack of early improvement with antipsychotics and subsequent non-response could provide a clinically relevant opportunity to discontinue medications that carry significant risk of harm in people with dementia and explore alternative treatment options (where available) at an early stage. This is critically important since the

use of antipsychotics can result in a variety of side effects,[5] including increased mortality.[5,7] Indeed, longer use of antipsychotics is associated with increased mortality[5,7] and there is also evidence that this association is dose-dependent.[7] In the light of these findings, the use of antipsychotics is not recommended as a first-line treatment for BPSD.[37] Despite these safety concerns, prescribing surveys have consistently shown the continuing and frequent use of antipsychotics for patients with severe BPSD, which clearly underscores the importance of the topic addressed by our study.[38] On the other hand, while the results of this study suggest clinical utility of discontinuing the medication that does not seem to provide any further benefit and trying a next treatment option, there is not any better evidence-supported therapy, which is a dilemma in the treatment of BPSD.

The results of our study must be interpreted in the light of some limitations. First, CATIE-AD was not originally designed to examine whether presence/absence of early improvement with antipsychotics could predict subsequent treatment outcomes. The association between early improvement and subsequent response was derived from a

post-hoc analysis; therefore, appropriate caution is required in interpretation of the results. Second, only patients treated with olanzapine, quetiapine, or risperidone, were included, which limits any extrapolation of our findings to other antipsychotics. Third, the potential influence of medication dose was not taken into consideration since flexible dosing was employed in this study. Fourth, the choice of weeks 2 and 8 for the timing of assessments was based on previous studies that have examined prediction performance in patients with schizophrenia and MDD,[15,17] but it may still be considered arbitrary. Fifth, other factors such as adverse events, which may work as predictors of poor subsequent response, were not taken into consideration in the present study since they were not evaluated in a systematic manner, using assessment scales. Further investigations focusing on the potential roles of adverse events in predicting subsequent outcomes are warranted. Sixth, the primary outcomes for this analysis were BPRS and NPI total scores. However, the total scores on these instruments include a broad range of symptoms and therefore may not always reflect treatment targets. Although we included dementia psychosis subtype as an independent variable in the logistic regression analysis for NPI and found no significant relationship in this regard, further investigations focusing on specific

symptoms are clearly needed. Seventh, although the odds ratios that predicted subsequent response were statistically significant, they were relatively small. Moreover, while accuracy of the prediction performance was found to be generally good, there still were many inaccuracies in the model. These results suggest that the response to antipsychotic treatment may not be easy to accurately predict solely based on early symptom improvement. In fact, treatment response has been reported to be associated with a number of factors, including genetic background.[39] Further investigations such as genetic studies to identify more detailed predictors for good treatment response in BPSD are warranted. Thus, the results of this study should be interpreted with caution in the clinical settings. Finally, there was a large amount of missing data for the BPRS and NPI scores at week 8 (i.e. 52.2% and 51.6%, respectively), which we addressed through the use of multiple imputation. Although this method is a valid approach to missing data,[40] and one which produced similar results for our main finding compared to available case analysis, we cannot be certain that the imputed data are completely representative of the original data. This is perhaps most relevant when considering the potential influence of medication dose and adverse events on drop-out and subsequent outcome. Furthermore,

since the CATIE design allowed participants to be transitioned to other treatments (i.e. switching from Phase 1 to Phase 2), clinical reasons for exit from Phase 1 were not randomly related with insufficient efficacy or adverse effects. Thus, those remaining in the study phase 1 may not be entirely representative of the group initially treated, which limits the generalizability of the findings in the present study. For these reasons, our observations should be viewed as preliminary and need to be confirmed in a prospective clinical trial.

In conclusion, presence/absence of early improvement at week 2 with antipsychotic treatment may be a predictor of subsequent response or non-response at week 8 in the treatment of BPSD, as has been shown to be the case for depression and schizophrenia. This finding indicates that, especially in light of higher NPVs, evaluating patients early in the course of treatment with antipsychotic drugs help identify non-responders who are unlikely to benefit from continuation of the current antipsychotic. Although future prospective studies are needed to confirm those preliminary findings, the results of this study underscore the relevance of focusing on symptom trajectories in guiding

antipsychotic treatment on an individual basis to minimize unwanted adverse effects in the treatment of BPSD.

References

1. Devanand DP, Jacobs DM, Tang MX, et al: The course of psychopathologic features in mild to moderate Alzheimer disease. Arch Gen Psychiatry 1997; 54:257-263

2. Seitz DP, Brisbin S, Herrmann N, et al: Efficacy and Feasibility of Nonpharmacological Interventions for Neuropsychiatric Symptoms of Dementia in Long Term Care: A Systematic Review. JMDA 2012; 13:503–506.e2

3. Maust DT, Langa KM, Blow FC, et al: Psychotropic use and associated neuropsychiatric symptoms among patients with dementia in the USA. Int J Geriat Psychiatry (in press)

4. Sultzer DL, Davis SM, Tariot PN, et al: Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. Am J Psychiatry 2008; 165:844-854

5. Schneider LS, Dagerman K, Insel PS: Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 2006; 14:191-210

6. Ballard C, Waite J: The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Ballard CG, ed. Cochrane Database Syst Rev 2006; (1):CD003476

7. Maust DT, Kim HM, Seyfried LS, et al: Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia. JAMA Psychiatry 2015; 72:438-445

8. US Food and Drug Administration. Public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. US Department of Health and Human Services. http: //www.fda.gov/Drugs/DrugSafety/ucm053171.htm. Accessed July 27, 2015

9. American Psychiatric Association (APA). Guideline watch (October 2014): practice guideline for the treatment of patients with Alzheimer’s disease and other dementias.

http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf. Accessed March 3, 2015

10. Uchida H, Mamo DC, Mulsant BH, et al: Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. J Clin Psychiatry 2009; 70:397-405

11. Uchida H, Mamo DC: Dosing of antipsychotics in schizophrenia across the life-spectrum. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33:917-920

12. Kinon BJ, Chen L, Ascher-Svanum H, et al: Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. Schizophr Res 2008; 102:230-240

13. Correll CU, Malhotra AK, Kaushik S, et al: Early prediction of antipsychotic response in schizophrenia. Am J Psychiatry 2003; 160:2063-2065

14. Szegedi A, Jansen WT, van Willigenburg APP, et al: Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. J Clin Psychiatry 2009; 70:344-353

15. Ascher-Svanum H, Nyhuis AW, Faries DE, et al: Clinical, Functional, and Economic Ramifications of Early Nonresponse to Antipsychotics in the Naturalistic Treatment of Schizophrenia. Schizophr Bull 2008; 34:1163-1171

16. Taylor D, Paton C, Kapur S: The Maudsley Prescribing Guidelines in Psychiatry, 11th Edition. New York, John Wiley & Sons, 2012

17. Tadić A, Helmreich I, Mergl R, et al: Early improvement is a predictor of treatment outcome in patients with mild major, minor or subsyndromal depression. J Affect Disord 2010; 120:86-93

18. Schneider LS, Ismail MS, Dagerman K, et al: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer's disease trial. Schizophr Bull 2003; 29:57-72

19. Schneider LS, Tariot PN, Lyketsos CG, et al: National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer disease trial methodology. Am J Geriatr Psychiatry 2001; 9:346-360

20. First MB: User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version. Washington, DC: American Psychiatric Association, 1997

21. McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939-944

22. Beller SA, Overall JE: The Brief Psychiatric Rating Scale (BPRS) in geropsychiatric research: II. Representative profile patterns. J Gerontol 1984; 39:194-200

23. Cummings JL, Mega M, Gray K, et al: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44:2308-2314

24. Reeves SJ, Clark-Papasavas C, Gould RL, et al: Cognitive phenotype of psychotic symptoms in Alzheimer's disease: evidence for impaired visuoperceptual function in the misidentification subtype. Int J Geriat Psychiatry 2015; 30:1147-1155

25. Cook SE, Miyahara S, Bacanu S-A, et al: Psychotic symptoms in Alzheimer disease: evidence for subtypes. Am J Geriatr Psychiatry 2003; 11:406-413

26. Howard R, Phillips P, Johnson T, et al: Determining the minimum clinically important differences for outcomes in the DOMINO trial. Int J Geriat Psychiatry 2010; 26:812-817

27. McGlothlin AE, Lewis RJ: Minimal clinically important difference: defining what really matters to patients. JAMA 2014; 312:1342-1343

28. Rubin DB: Multiple Imputation for Nonresponse in Surveys. New York, John Wiley & Sons, 1987

29. Uchida H, Takeuchi H, Graff-Guerrero A, et al: Dopamine D2 Receptor Occupancy and Clinical Effects. J Clin Psychopharmacol 2011; 31:497-502

30. Leucht S, Busch R, Kissling W, et al: Early prediction of antipsychotic nonresponse among patients with schizophrenia. J Clin Psychiatry 2007; 68:352-360

31. Katz MM, Tekell JL, Bowden CL, et al: Onset and Early Behavioral Effects of Pharmacologically Different Antidepressants and Placebo in Depression. Neuropsychopharmacology 2003; 29:566-579

32. Szegedi A, Müller MJ, Anghelescu I, et al: Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. J Clin Psychiatry 2003; 64:413-420

33. Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261-276

34. Potkin SG, Gharabawi GM, Greenspan AJ, et al: A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. Schizophr Res 2006; 85:254-265

35. Leucht S, Rothe P, Davis JM, et al. Equipercentile linking of the BPRS and the PANSS. Eur Neuropsychopharmacol 2013; 23:956-959

36. Ballard C, Corbett A, Howard R: Prescription of antipsychotics in people

with dementia. Br J Psychiatry 2014; 205:4-5

37. Azermai M, Petrovic M, Elseviers MM, et al: Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms. Ageing Res Rev 2012; 11:78-86

38. Mitka M: CMS seeks to reduce antipsychotic use in nursing home residents with dementia. JAMA 2012; 308:119-121

39. Baou M, Boumba VA, Petrikis P, et al: A review of genetic alterations in the serotonin pathway and their correlation with psychotic diseases and response to atypical antipsychotics. Schizophr Res 2016; 170:18-29

40. Little RJ, D'Agostino R, Cohen ML, et al: The prevention and treatment of missing data in clinical trials. N Engl J Med 2012; 367:1355-1360