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The need for individualised antipsychotic drug therapy in patients with schizophrenia

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Abstract. – Drug therapy for schizophrenia aims to both reduce symptoms in the acute phase and maintain long-term symptomatic remission during periods of stabilization. Atypical antipsychotic agents are the mainstay of schizophrenia therapy because of their improved tolerability, including a reduced likelihood of extrapyramidal symptoms, compared with conventional antipsychotics. However, responses to antipsychotic therapy are influenced by a wide range of factors, such as age, gender, race, comorbidities, genetics and social and environmental conditions, that make identifying the most appropriate antipsychotic treatment for each individual patients, an ongoing challenge for physicians. Tools that may be useful to assist clinicians in determining appropriate individual therapy include consideration of treatment moderators, which specify for whom or under what conditions a treatment works, treatment mediators, which are mechanisms by which a treatment achieves its effects, and cluster group analyses, which identify subsets of patients with similar characteristics. Further research is required to determine whether cluster groups of patients with schizophrenia can be identified based on treatment moderators and mediators, and whether antipsychotic prescribing based on consideration of these cluster groups leads to improved treatment outcomes.

Key Words:

Antipsychotics, Cluster analysis, Mediators, Moderators, Schizophrenia.

Introduction

Schizophrenia, along with schizoaffective disorders and other psychotic conditions, is one of an array of chronic, recurrent, psychotic disorders that are estimated to affect almost 1% of the population worldwide[1,2]. The diagnostic and statistical manual of mental disorders (DSM-IV-TR) specifies five main subtypes of schizophrenia, which are characterized by a complex range of symptoms[1,3-5]. Dangerous behaviours during acute episodes can cause severe emotional distress and may put the patient and others at risk of harm[5]. In the long term, repeated hospital visits, ongoing rehabilitation, and continual therapy can impair patients' health-related quality of life (HRQL)[1,6,7].

Drug treatment for schizophrenia aims to both eliminate or reduce symptoms during acute episodes, and maintain long-term symptomatic remission[1,5,8]. Conventional antipsychotic agents formed the mainstay of schizophrenia therapy until the introduction of clozapine, the first atypical antipsychotic, in 1989. Eight other atypical antipsychotics have subsequently been approved for use in schizophrenia therapy (amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, sertindole and ziprasidone). Generally, atypical antipsychotics confer improved tolerability, compared with conventional agents, including a lower risk of extrapyramidal symptoms (EPS), tardive dyskinesia and serum prolactin elevation[9-11]. Consequently, these agents are preferred for first-line therapy of acute schizophrenia episodes[5,12]. Atypical antipsychotics are also effective for long-term maintenance therapy and can reduce the risk of relapse to below 30% per year[5].

The high variability of human brain activity and resulting behaviours influence individual responses to antipsychotic therapy, from complete remission of positive symptoms to absolute refractoriness[13]. Dosage adjustments or switches to other antipsychotic agents may be required to achieve an optimal response. However, treatment changes are complicated by a lag time of up to 4 weeks before a significant response is seen; full treatment responses may not be observed for 6 months[5].

Tools to aid clinicians in prescribing individualised therapy based on the pharmacological characteristics of antipsychotics have been suggested. In 2007, an expert consensus panel produced a roadmap for antipsychotic treatment

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based on an integrated approach combining clinical evidence with pharmacological characteristics of antipsychotic agents[8]. More recently, the landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study has provided practical information about the comparable utility of antipsychotic agents in a clinical practice setting[14]. Although the results were controversial, in that 74% of patients discontinued antipsychotic treatment before 18 months because of lack of efficacy or poor tolerability and clozapine was the most effective agent for patients who had discontinued treatment because of lack of efficacy[14], they contain valuable lessons for clinical practice that are still being realised.

However, individualised antipsychotic therapy is extremely difficult to achieve in practice because of the broad range of factors that may influence outcomes. In addition to pharmacological characteristics, other factors that might influence treatment outcomes include: disease characteristics, such as the phase of illness; treatment history, including the likelihood of adherence and history of substance abuse problems; demographic characteristics such as age and gender; and social and environmental factors such as homelessness or inadequate access to medical services[8].

Kraemer et al[15] proposed that factors that determine treatment outcomes can be considered either as moderators or mediators. In addition, cluster analysis, the collective term for various multivariate methods that attempt to identify homogeneous cases or observations ('clusters') in raw data, has been applied to a variety of research questions in medicine, including schizophrenia[16-21]. By enabling the empirical classification of patients with similar characteristics into cluster groups, cluster analytical techniques could assist physicians in selecting individualized antipsychotic treatment based on patients' personal characteristics, thereby improving treatment outcomes.

This article considers how combining the concepts of mediators, moderators and cluster analyses could be useful to better understand how antipsychotic therapy could be individualised. A discussion of potential moderators or mediators is provided, followed by a review of two studies in schizophrenia patients that have utilised cluster group analyses to identify specific patients and treatment characteristics.

Moderators

Moderators of antipsychotic therapy are those factors that determine for whom, or under what conditions, a treatment will be effective [15] . Moderators exist prior to the initiation of therapy and affect the relationship between the treatment and the outcome. In the clinical trial setting, moderators are present at baseline or prior to randomization.

Based on this definition, moderators of antipsychotic treatment outcomes are likely to include a variety of individual patient characteristics[5,22]. Gender is an important influence of response. Males are more likely to experience early-onset schizophrenia and display negative symptoms, whereas females are more likely to experience positive symptoms and are more likely to experience a rapid and complete response to antipsychotic therapy[22,23]. Age also moderates response; adolescent patients with early-onset schizophrenia experience progressive grey matter loss and their symptoms, and therefore treatment needs, may change over time [24]. Older patients are more likely to be receiving treatment for concomitant conditions such as dementia or Parkinson's disease, and are at an increased risk of tardive dyskinesia related to antipsychotic therapy[5,25,26]. Other comorbidities, such as cardiovascular and respiratory diseases, diabetes, and other personality disorders, are highly prevalent among schizophrenic patients. In addition to contributing to a high non-suicide-related mortality rate, these conditions may reduce adherence to therapy[5,27] . Patient preference and/or prior drug experience are other key determinants of treatment selection and, therefore, response[1,5].

Moderators may also comprise wider social and environmental factors that indirectly affect outcomes by affected treatment adherence. Adherence to antipsychotic therapy is notoriously poor. Only 52% of US patients with bipolar disorder were fully adherent, according to a recent review[28]. Patients who have a history of poor compliance may not respond well to treatment switching or dose titrations[26-28]. Adherence may also be compromised if patients choose to avoid medication during the acute phase to prolong the perceived benefits of the manic state; approximately 60% of patients may be nonadherent during acute mania[29]. As many as 50% of schizophrenic patients have a substance abuse disorder, which can exacerbate concomitant conditions such as depression, and further increase the likelihood of nonadherence because of added financial burdens, housing instability and family pressures[5,27]. Racial and ethnic minority groups are more likely to receive antipsychotic therapy with

dosages above the recommended levels[30-33], which can increase the likelihood of EPS and, consequently, poor adherence, as side effects are a common reason for treatment discontinuation[5,34].

Metabolic abnormalities, including weight gain and an increased risk of dyslipidaemia and diabetes, are associated with antipsychotic therapy and can moderate the outcome of therapy by influencing adherence. Diabetes and obesity are up to two times more prevalent among schizophrenic patients than in the general population[1,35,36]. There may be a genetic predisposition to atypical antipsychotic therapy-associated weight gain arising from mutation in key metabolic genes, although more research is required to determine the exact role of genetics in this area[37-40]. The risk of metabolic effects may be associated with the receptor binding profile; histamine H_1 receptor antagonism is correlated with weight gain[41].

Genetic variation may also moderate individual treatment responses. A high rate of success with clozapine treatment is associated with an optimal combination of six gene variations[26,42]. The cytochrome P450 (CYP450) isoenzyme CYP2D6 is implicated in the metabolism of atypical antipsychotics, and patients with genetic deficiency in CYP2D6 metabolism have higher plasma drug concentrations and an increased risk of adverse effects[26,42]. It has recently been suggested that individual differences in disease and patient characteristics should be considered in the methodology for pharmacogenetic studies in patients with conditions such as depression[43]; a similar approach is useful in patients with schizophrenia.

Mediators

Mediators are, according to the definition posited by Kraemer et al, causal mechanisms by which a treatment might achieve its effects[15]. They are factors that occur during treatment to determine individual differences in response to treatment.

Differences between antipsychotic agents in clinical efficacy, tolerability and pharmacological and pharmacokinetic characteristics can be considered mediators. Currently, there is limited evidence to support the superior efficacy of any single atypical antipsychotic agent over another[1,5,44]. The recent Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study compared a first-generation agent (perphenazine) with the atypical antipsychotics: olanzapine, quetiapine, risperidone and ziprasidone[14,44,45]. Results from the first phases of the study, in 1460 patients, indicated that olanzapine was superior to perphenazine and ziprasidone in terms of time to discontinuation, despite substantial metabolic adverse effects associated with this agent[14]. A subsequent analysis of data from 99 patients who had discontinued treatment with atypical antipsychotics found that, surprisingly, clozapine was significantly more effective than other atypical agents. Although they are conflicting, these results are considered broadly consistent with data both from recent clinical trials and from practical experience[44].

Antipsychotic agents vary in chemical structure, receptor binding affinities and pharmacokinetic properties[8,46-48]. They have a narrow therapeutic window of striatal dopamine D_2 receptor occupancy. D_2 receptor occupancy is required to be at least 65% for antipsychotic efficacy, but >80% occupancy produces EPS[8,46,49]. A correlation between plasma drug concentrations and dopamine D_2 receptor occupancy has been observed, and optimal therapeutic concentrations have been identified for clozapine (350-600 ng/mL), risperidone (20-60 ng/mL) and olanzapine (20-80 ng/mL)[50]. The rate of dissociation from D_2 receptors may also determine the likelihood of EPS. Clozapine and quetiapine have fast dissociation rates and have a reduced risk of EPS[47].

The time taken for the drug to reach the receptor mediates treatment response[1,10,46,47]. Long-acting injectable formulations, such as risperidone long-acting and olanzapine pamoate depot injection, and oral extended-release formulations, such as paliperidone ER and quetiapine fumarate XR, generally have more consistent peak-to-trough plasma levels and availability to receptors. These characteristics could improve outcomes by providing sustained plasma drug concentrations within the therapeutic window[9].

Polypharmacy with different antipsychotic agents may also mediate outcomes by increasing the risk of suboptimal efficacy and adverse effects resulting from drug-drug interactions and altered plasma drug levels and pharmacokinetic profiles[26,48,51,52]. Drug plasma concentrations may be influenced by inhibitors or inducers of antipsychotic metabolism. For example, clozapine concentrations are increased when it is co-administered with selective serotonin inhibitors that inhibit CYP2D6 activity, such as fluoxetine, parox-

etine or sertraline[8]. In addition, co-administration of fluvoxamine appears to be associated with a 5- to 10-fold increase in the steady-state plasma concentration of clozapine[53-57].

Cluster Analyses

Two studies have applied cluster analyses in patients with schizophrenia to determine predictors of neurological performance[16] and attitudes to medication that affect compliance[21].

Goldstein et al[16] utilized a cluster analysis method to determine the effect of antipsychotic medication on neurological performance. A total of 80 patients with DSM-IV-diagnosed schizophrenia or schizoaffective disorder were classified according to their performance on the Neurologic Evaluation Scale, either while on or off antipsychotic medication. Three clusters were identified: normal, cognitively impaired, and diffusely impaired. Among patients off antipsychotic therapy, 44% had normal neurological performance, 44% had specific cognitive and/or perceptual impairment, and12% had generalized impairment; corresponding proportions among patients on antipsychotic therapy were 55%, 20% and 25%. External validity analyses revealed that, among on-treatment patients, cluster membership was linked to current age and age at schizophrenia onset. Patients with diffuse impairment were older at the time of disease onset than patients in the other clusters. Among off-treatment patients, cluster membership was related to psychiatric status (according to Brief Psychiatric Rating Scale score), general intelligence and education[16]. Although these data are preliminary and require confirmation from other studies, they indicate that the classification of patients into clusters based on their neurological performance may reveal specific characteristics such as age at onset of schizophrenia that may act as moderators of treatment outcomes.

The study by Santone et al[21] utilized a cluster technique to investigate attitudes to medication among 99 hospital inpatients with schizophrenia. Using scores from the Rating of Medication Influences scale and other questionnaires, the Authors applied cluster analyses to reveal that patients' attitudes to medication could be categorized into four clusters. These were: (1) ambivalence (22%); (2) problems with patient, family, alliance [characterized by negative personal attitudes and negative external drives] (14.3%); (3) medication affinity, positive influence from others (39%); and (4) illness, medication, label distress [including patients with a high level of personal distress arising from the social stigma attached to medication] (24.7%). These results led the Authors to conclude that interventions to improve attitudes to medicine, and thereby improve compliance, could be targeted to address the needs of each cluster. For example, the fear of stigma observed in patients in cluster 4 could be addressed by encouraging social integration to alleviate their sense of isolation[21]. Attitudes to medication are another example of moderators that can affect treatment outcomes.

Moderators, Mediators and Cluster Groups: Tools for Individualizing Therapy?

An understanding of moderators and mediators of treatment outcomes, and cluster groups based on similar moderators and mediators, could assist clinicians to better understand how an individual patient will respond to antipsychotic therapy.

Recognition of treatment moderators with similar effects on outcomes could lead to the identification of clusters of patients likely to experience similar outcomes. Patient symptom profiles are a logical target for grouping similar mediators. Antipsychotic response can be predicted according to whether symptoms are primarily positive, negative or general in nature, based on the Positive and Negative Syndrome Scale[58]. Positive symptoms include delusions, hallucinations, hostility, and disorganized thinking, whereas negative symptoms include emotional and social withdrawal, poverty of speech and amotivation. General cognitive symptoms are those such as impaired attention, short-term memory and verbal function. As discussed above, females may be more likely to experience positive symptoms while males may be more likely to display negative symptoms. It would be useful to investigate whether patients can be grouped into clusters based on their symptom profile, and whether different clusters are predictive of different responses to various antipsychotic agents.

Similarly, clusters of mediators with similar characteristics could be identified. Antipsychotic agents could be grouped according to pharmacodynamic characteristics, such as neurotransmitter binding affinity (Figure 1) or location of activity in the frontal cortex and striatum[59-61]. For example, haloperidol acts mainly on striatal dopaminergic receptors, whereas clozapine acts primarily at serotonergic receptors and has limited activity at dopamine receptors. Agents could also be

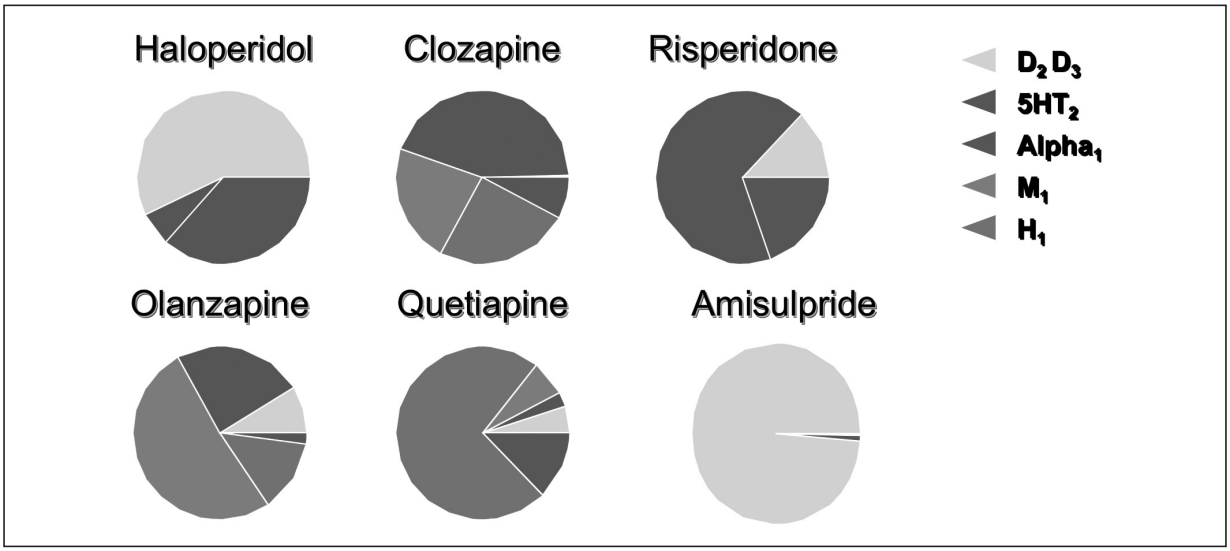

Figure 1. Different binding affinities of various antipsychotic agents[59,61].

clustered based on whether it is necessary to conduct therapeutic drug monitoring to establish optimal plasma drug concentrations for maximum efficacy or tolerability [62].

Presently there are no data on the use of cluster groups based on mediators or moderators in patients with schizophrenia. Further investigations are required to determine firstly whether cluster groups can be identified based on the mediators and moderators suggested here, and secondly whether consideration of these cluster groups by clinicians prescribing antipsychotic therapy affects treatment outcomes.

Conclusions

In conclusion, the selection of appropriate drug therapy for schizophrenia is complicated by the wide range of patients and treatment factors that may affect responses. Identification of cluster groups of patients with schizophrenia based on moderators and mediators of outcomes could assist clinicians in identifying patients who are likely to achieve a response or who will be compliant with therapy. Further research is required to determine whether cluster groups can be identified based on treatment moderators and mediators, and whether antipsychotic prescribing based on consideration of these cluster groups leads to optimal treatment outcomes.

References

1) Noel JM. ASHP therapeutic position statement on the use of second-generation antipsychotic medications in the treatment of adults with psychotic disorders. Am J Health Syst Pharm 2007; 64: 863-876.

2) Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, just the facts: what we know in 2008 part 1: overview. Schizophr Res 2008; 100: 4-19.

3) APA. Schizophrenia and other psychotic disorders. 4th ed. Washington DC: American Psychiatric Press; 2000.

4) Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 2007; 13: 261-276.

5) Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiat 2004; 161(2 Suppl): 1-56.

6) Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2005; 66: 1205-1215.

7) Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51: 8-19.

8) Weiden PJ, Preskorn SH, Fahnestock PA, Carpenter D, Ross R, Docherty JP. Translating the psychopharmacology of antipsychotics to individualized treat-

ment for severe mental illness: a Roadmap. J Clin Psychiatry 2007; 68(Suppl 7): 1-48.

9) Conley RR, Kelly DL. Second-generation antipsychotics for schizophrenia: a review of clinical pharmacology and medication-associated side effects. Isr J Psychiatry Relat Sci 2005; 42: 51-60.

10) Derry S, Moore RA. Atypical antipsychotics in bipolar disorder: systematic review of randomised trials. BMC Psychiatry 2007; 7: 40.

11) Pierre JM. Extrapyramidal symptoms with atypical antipsychotics: incidence, prevention and management. Drug Safety 2005; 28: 191-208.

12) Weiden PJ. Switching antipsychotics: an updated review with a focus on quetiapine. J Psychopharmacol 2006; 20: 104-119.

13) Emsley RA. Partial response to antipsychotic treatment: the patient with enduring symptoms. J Clin Psychiatry 1999; 60(Suppl 23): 10-13.

14) Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353: 1209-1223.

15) Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry 2002; 59: 877-883.

16) Goldstein G, Sanders RD, Forman SD, Tarpey T, Gurklis JA, Van Kammen DP, Keshavan MS. The effects of antipsychotic medication on factor and cluster structure of neurologic examination abnormalities in schizophrenia. Schizophr Res 2005; 75: 55-64.

17) Hartigan J. Clustering algorithms. New York: Wiley; 1975.

18) Helmes E, Landmark J. Subtypes of schizophrenia: a cluster analytic approach. Can J Psychiatry 2003; 48: 702-708.

19) Hoti F, Tuulio-Henriksson A, Haukka J, Partoen T, Holmstrom LJL. Family-based clusters of cognitive test performance in familial schizophrenia. BMC Psychiatry 2004; 4: 1-13.

20) Lencz T, Raine A, Sheard C. Neuroanatomical bases of electrodermal hypo-responding: a cluster analytic study. Int J Psychophysiol 1996; 665.

21) Santone G, Rucci P, Muratori ML, Monaci A, Ciarafoni C, Borsetti G. Attitudes toward medication in inpatients with schizophrenia: a cluster analytic approach. Psychiatry Res 2008; 158: 324-334.

22) Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand Suppl 2000; 401: 3-38.

23) Szymanski S, Lieberman JA, Alvir JM, Mayerhoff D, Loebel A, Geisler S, Chakos M, Koreen A, Jody D, Kane J, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. Am J Psychiatry 1995; 152: 698-703.

24) Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R, Taga AW, Rapoport JL. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proc Natl Acad Sci U S A 2001; 98: 11650-11655.

25) Bjerrum L, Sogaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. Eur J Clin Pharmacol 1998; 54: 197-202.

26) Kim E, Levy R, Pikalov A. Personalized treatment with atypical antipsychotic medications. Adv Ther 2007; 24: 721-740.

27) Gianfrancesco FD, Rajagopalan K, Sajatovic M, Wang RH. Treatment adherence among patients with bipolar or manic disorder taking atypical and typical antipsychotics. J Clin Psychiatry 2006; 67: 222-232.

28) Sajatovic M, Valenstein M, Blow FC, Ganoczy D, Ignacio RV. Treatment adherence with antipsychotic medications in bipolar disorder. Bipolar Disord 2006; 8: 232-241.

29) Lingham R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatr Scand 2002; 105: 164-172.

30) Diaz FJ, De Leon J. Excessive antipsychotic dosing in 2 U.S. State hospitals. J Clin Psychiatry 2002; 63: 998-1003.

31) Segal SP, Bola JR, Watson MA. Race, quality of care, and antipsychotic prescribing practices in psychiatric emergency services. Psychiatr Serv 1996; 47: 282-286.

32) Walkup JT, McAlpine DD, Olfson M, Labay LE, Boyer C, Hansell S. Patients with schizophrenia at risk for excessive antipsychotic dosing. J Clin Psychiatry 2000; 61: 344-348.

33) Wheeler A, Humberstone V, Robinson E. Ethnic comparisons of antipsychotic use in schizophrenia. Aust N Z J Psychiatry 2008; 42: 863-873.

34) Kane JM. Extrapyramidal side effects are unacceptable. Eur Neuropsychopharmacol 2001; 11(Suppl. 4): S397-403.

35) Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156: 1686-1696.

36) American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 2004; 65: 267-272.

37) Mill J, Tang T, Kaminsky Z, Khare T, Yazdanpanah S, Bouchard L, Jia P, Assadzadeh A, Flanagan J, Schumacher A, Wang SC, Petronis A. Epigenomic profiling reveals DNA-methylation changes associated

with major psychosis. Am J Hum Genet 2008; 82: 696-711.

38) Muller DJ, Muglia P, Fortune T, Kennedy JL. Pharmacogenetics of antipsychotic-induced weight gain. Pharmacol Res 2004; 49: 309-329.

39) Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet 2002; 359: 2086-2087.

40) Serretti A, Mandelli L. The genetics of bipolar disorder: genome "hot regions", genes, new potential candidates and future directions. Mol Psychiatry 2008; 13: 742-771.

41) Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Mol Psychiatry 2008; 13: 27-35.

42) Arranz MJ, Munro J, Birkett J, Bolonna A, Mancama D, Sodhi M, Lesch KP, Meyer JF, Sham P, Collier DA, Murray RM, Kerwin RW. Pharmacogenetic prediction of clozapine response. Lancet 2000; 355: 1615-1616.

43) Serretti A, Kato M, Kennedy JL. Pharmacogenetic studies in depression: a proposal for methodologic guidelines. Pharmacogenomics J 2008; 8: 90-100.

44) Swartz MS, Stroup TS, McEvoy JP, Davis SM, Rosenheck RA, Keefe RS, Hsiao JK, Lieberman JA. What CATIE found: results from the schizophrenia trial. Psychiatry Serv 2008; 59: 500-506.

45) Manschreck TC, Boshes RA. The CATIE schizophrenia trial: results, impact, controversy. Harv Rev Psychiatry 2007; 15: 245-258.

46) Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol Psychiatry 2001; 50: 873-883.

47) Pani L, Pira L, Marchese G. Antipsychotic efficacy: relationship to optimal D2-receptor occupancy. Eur Psychiatry 2007; 22: 267-275.

48) Sharif ZA. Pharmacokinetics, metabolism, and drug-drug interactions of atypical antipsychotics in special populations. Primary Care Companion J Clin Psychiatry 2003; 5(Suppl 6): 22-25.

49) Kapur S, Zipursky R, Jones C. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000; 157: 514-520.

50) Hiemke C, Dragicevic A, Gründer G, Hätter S, Sachse J, Vernaleken I, Müller MJ. Therapeutic monitoring of new antipsychotic drugs. Ther Drug Monit 2004; 26: 156-160.

51) Ananth J, Parameswaran S, Gunatilake S. Antipsychotic polypharmacy. Curr Pharm Des 2004; 10: 2231-2238.

52) Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. Curr Med Chem 2004; 11: 313-327.

53) Dequardo JR, Roberts M. Elevated clozapine levels after fluvoxamine initiation. Am J Psychiatry 1996; 153: 840-841.

54) Hiemke C, Weigmann H, Hartter S, Dahmen N, Wetzel H, Muller H. Elevated levels of clozapine in serum after addition of fluvoxamine. J Clin Psychopharmacol 1994; 14: 279-281.

55) Jerling M, Lindstrom L, Bondesson U, Bertilsson L. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. Ther Drug Monit 1994; 16: 368-374.

56) Koponen HJ, Leinonen E, Lepola U. Fluvoxamine increases the clozapine serum levels significantly. Eur Neuropsychopharmacol 1996; 6: 69-71.

57) Markowitz JS, Gill HS, Lavia M, Brewerton TD, DeVane CL. Fluvoxamine-clozapine dose-dependent interaction. Can J Psychiatry 1996; 41: 670-671.

58) Dikeos DG, Wickham H, McDonald C, Walshe M, Sigmundsson T, Bramon E, Grech A, Toulopoulou T, Murray R, Sham PC. Distribution of symptom dimensions across Kraepelinian divisions. Br J Psychiatry 2006; 189: 346-353.

59) Richelson E. Preclinical pharmacology of neuroleptics: focus on new generation compounds. J Clin Psychiatry 1996; 57(Suppl 11): 4-11.

60) Seeger TF, Seymour PA, Schmidt AW, Zorn SH, Schulz DW, Lebel LA, McLean S, Guanowsky V, Howard HR, Lowe JA 3rd, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995; 275: 101-113.

61) Westerink BH, Kawahara Y, De Boer P, Geels C, De Vries JB, Wikström HV, Van Kalkeren A, Van Vliet B, Kruse CG, Long SK. Antipsychotic drugs classified by their effects on the release of dopamine and noradrenaline in the prefrontal cortex and striatum. Eur J Pharmacol 2001; 412: 127-138.

62) Mauri MC, Volonteri LS, Colasanti A, Fiorentini A, De Gaspari IF, Bareggi SR. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet 2007; 46: 359-388.

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