•Forum•

Decreasing antipsychotic polypharmacy

Psychopharmacological treatment for schizophrenia: less is more

Chuanyue WANG

Summary: Antipsychotic polypharmacy in the treatment of schizophrenia is more common in China and other Asian countries than in Western countries. The reasons for this are unclear, but it may be related to an unsubstantiated belief among clinicians that multiple medications are more likely to achieve the desired clinical outcome. Antipsychotic medications are the mainstay of treatment for individuals with schizophrenia, but the use of antipsychotic polypharmacy and of high dosages of antipsychotic medication are associated with substantially increased risks without conferring improved clinical outcomes. It is generally accepted that high dosages of antipsychotic medications and the simultaneous use of multiple antipsychotics are associated with an increased prevalence, duration, and severity of adverse drug effects. More recent evidence also suggests that antipsychotic polypharmacy and the associated high overall dosage of antipsychotic medication lead to excessive striatal D2 receptor occupation (resulting in tolerance and drug withdrawal problems) and exacerbation of the impaired synaptic plasticity seen in schizophrenia (magnifying the cognitive impairment associated with the condition). Clinicians need to apply the 'less is more' principle in the psychopharmacological treatment of schizophrenia.

Keywords: antipsychotic polypharmacy; cognitive impairment; low-dose antipsychotic medication; synaptic plasticity

[*Shanghai Arch Psychiatry.* 2015; **27**(6): 368-370. Epub 2015 Nov 10. doi: http://dx.doi.org/10.11919/j.issn.1002-0829.215086]

At the 2014 annual meeting of the European College of Neuropsychopharmacology (ECNP) Professor Lieuwe de Haan from the University of Amsterdam presented support for the 'less is more' approach to the use of antipsychotic medication in patients with schizophrenia, describing strategies for low-dose and time-limited treatments.[1] Understanding and implementing this principal in clinical practice will help standardize psychopharmacological treatments for schizophrenia and improve outcomes for patients.

Antipsychotic polypharmacy is more widespread in Asia (32%) and Europe (26%) than in North America (16%).[2] A multi-country study, the Research on Asian Psychotropic Prescription Pattern (REAP) program,[3] reported lower rates of polypharmacy with multiple antipsychotics in China than the average rate in other parts of Asia, both in 2001 (25% versus 47%) and in 2009 (36% versus 43%).[3] A separate study in ten Chinese provinces in 2006 reported that 24% (1439/5898) of psychiatric inpatients and outpatients prescribed antipsychotic medications were being simultaneously treated with two or more antipsychotic medications and that 54% (3191/5898) were using adjunctive anticholinergic agents, benzodiazepines, β-receptor antagonists, antidepressants, or mood stabilizers.[4]

Antipsychotic polypharmacy is not well supported by evidence-based research. On the contrary, some studies suggest that it is associated with increased admissions, longer hospital stays, higher total dosages, more frequent and severe adverse reactions, higher treatment costs, and greater mortality.[5] The most common clinical rationale for antipsychotic polypharmacy is to improve clinical outcomes when the use of a single antipsychotic has only limited effectiveness and to make a slow transition from one medication to a second medication.[5] A 2009 meta-analysis[6] found that addition of a second antipsychotic medication could improve clinical outcomes if the initial (non-clozapine) antipsychotic medication only had limited benefit; however, these results were no longer statistically significant when studies from China were removed from the pooled sample.[6] Current practice

Beijing Anding Hospital, Beijing, China

correspondence: wang.cy@163.net

A full-text Chinese translation of this article will be available at http://dx.doi.org/10.11919/j.issn.1002-0829.215086 on December 25, 2015.

guidelines for the treatment of schizophrenia from the American Psychiatric Associations[7] recommend monotherapy with clozapine if monotherapy with other antipsychotic medications is ineffective; only after a full trial with clozapine proves ineffective should antipsychotic polypharmacy or the use of adjunctive psychopharmacological agents be considered. The Schizophrenia Patient Outcomes Research Team (PORT)[8] reported that the adjunctive use of antidepressants to treat acute depressive symptoms (but not negative psychotic symptoms) in persons with schizophrenia may be of use, but there is no evidence supporting the use of anti-anxiety medications to treat psychotic agitation in persons with schizophrenia. In fact, a Finnish study showed that the use of benzodiazepines significantly increased the mortality rates of patients with schizophrenia (HR, 1.91; 95% CI, 1.13-3.22).[9] Overall, monotherapy with antipsychotic medications must be the first choice for the clinical treatment of schizophrenia. In other words, 'less is more'.

Another related problem is the use of high or 'super-high' dosages of antipsychotic medication, a situation that is common when more than one antipsychotic medication is being administered. Lower efficacy of first-generation antipsychotic medications may be one of the reasons for their common use at high dosages, as clinicians try to improve outcomes by increasing dosages. High-dose medications unquestionably increase the prevalence, duration, and severity of adverse drug reactions, but there is no evidence that they actually improve clinical outcomes. A meta-analysis in 2000 showed that both the efficacy and tolerance of daily use of first generation antipsychotic medications such as haloperidol >12mg or its equivalent were worse than for second generation antipsychotic medications.[10]

The presumed mechanism of action of anti-psychotic medications is to block dopamine receptors. However, very high striatal D2 receptor occupancy is associated with more severe negative symptoms, depression, and non-adherence with medication.[11] Preliminary evidence suggests that the optimal striatal D2 receptor occupancy is in the range of 60 to 70%; this can usually be achieved with a daily dosage of haloperidol or risperidone of 2 to 4 mg or of olanzapine of 10 to 20 mg.[1,11] Higher levels of dopamine receptor occupancy increase the activation threshold of the receptor, and, thus, cause tolerance and dependence which makes it difficult to subsequently reduce the dosage or stop the medication.

Schizophrenia is a neurodevelopmental disorder with reduced synaptic plasticity; so it is important to ensure that the treatments for schizophrenia do not exacerbate this cognitive impairment. Animal studies have shown that the acute administration of most antipsychotic medications (excluding clozapine and olanzapine) is associated with impairments in long-term potentiation (LTP) and specific cognitive abilities.[12] This suggests that the use of antipsychotic medication in individuals with schizophrenia, particularly high-dose medication, may cause irreversible impairment of synaptic plasticity and, thus, gradual cognitive decline. Clinicians must make every effort to use the lowest dosage of antipsychotic medication possible to limit the risk or severity of these negative outcomes. Less is more.

The opposite danger is that these concerns will encourage patients, their family members, and psychiatrists to reduce the dosage or stop the use of antipsychotic medications too early in the course of treating an acute episode of illness. There is a strong global consensus among psychiatrists that patients with schizophrenia, like those with diabetes and hypertension, have a chronic illness that needs to be continuously treated – not only when acute symptoms arise – with appropriate medication.[7] There may be as many as 20% of individuals who meet formal diagnostic criteria of schizophrenia but recover fully with psychopharmacological treatment and, thus, no longer need medication. But at present there are no validated indicators that can identify these 'good prognosis' patients, so clinicians treating persons with schizophrenia should be very cautious when attempting to stop their antipsychotic medications.

Application of the 'less is more' principle in the treatment of patients with first-episode schizophrenia will lessen medication-related impairment, increase adherence, and support the more rapid recovery of cognitive and social functioning. Starting treatment with this approach will also make it easier to reduce dosages after the acute symptoms have receded and, for a subgroup of patients, to eventually stop antipsychotic medication altogether.

Funding

The preparation of this manuscript was not supported by any funding agency.

Conflict of interest statement

The author reports no conflict of interest related to this manuscript.

精神分裂症药物治疗的“物稀为贵”

王传跃

概述：在中国和其它亚洲国家中用抗精神病药联合治疗精神分裂症要比在西方国家更为常见，其原因尚不清楚，可能与临床医生的盲目信念有关，即认为用多种药物治疗更可能获得满意的临床疗效。抗精神病药物是治疗精神分裂症患者的主要方法，但抗精神病药物的联用及大剂量使用只会大幅增加风险而不会提高临床疗效。人们普遍认为大剂量使用抗精神病药以及多药联用与药物不良反应的发生率增加、持续时间延长、程度更严重等相关。新近的研究证据还表明，抗精神病药联用及抗精神病药物总剂量相应增高会导致较高的纹状体 D2 受体占有率（致使药物耐受及停药困难），并使精神分裂症中已受损的突触可塑性恶化（使与此状态相关的认知功能损害“雪上加霜”）。临床医生需要在精神分裂症的精神药物治疗中遵循“物稀为贵”的原则。

关键词：抗精神病药联用；认知功能障碍；低剂量抗精神病药物；突触可塑性

本文全文中文版从 2015 年 12 月 25 日起在 http://dx.doi.org/10.11919/j.issn.1002-0829.215086 可供免费阅览下载

References

1. De Haan L. Low-dose and time-limited antipsychotic treatment strategies in schizophrenia. *Eur Neuropsychopharm*. 2014; **24**(Suppl2): S134. doi: http://dx.doi.org/10.1016/S0924-977X(14)70182-8
2. Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. *Schizophr Res*. 2012; **138**(1): 18–28. doi: http://dx.doi.org/10.1016/j.schres.2012.03.018
3. Xiang YT, Wang CY, Si TM, Lee EH, He YL, Ungvari GS, et al. Antipsychotic polypharmacy in inpatients with schizophrenia in Asia (2001-2009). *Pharmacopsychiatry*. 2012; **45**(1): 7-12. doi: http://dx.doi.org/10.1055/s-0031-1286345
4. Si TM, Shu L, Yu X, Ma C, Wang GH, Bai PS, et al. [The second cross-sectional study on antipsychotic drug patterns of schizophrenia in China]. *Zhong Hua Jing Shen Ke Za Zhi*. 2010; **43**(1): 31-36. Chinese. doi: http://dx.chinadoi.cn/10.3760/cma.j.issn.1006-7884.2010.01.010
5. Barnes TR, Paton C. Antipsychotic polypharmacy in schizophrenia: benefits and risks. *CNS Drugs*. **2011; 25**(5): 383-399. doi: http://dx.doi.org/10.2165/11587810-000000000-00000
6. Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophr Bull*. 2009; **35**(2): 443–457. doi: http://dx.doi.org/10.1093/schbul/sbn018
7. American Psychiatry Association (APA) [online]. *Practice Guidelines for the Treatment of Patients with Schizophrenia, 2nd Edition.* 2004; Available from: http://www.psych.org/psych_pract/treatg/pg/SchizPG-Complete-Feb04.pdf [Accessed 2015]
8. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010; **36**(1): 71–93. doi: http://dx.doi.org/10.1093/schbul/sbp116
9. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Arch Gen Psychiatry*. 2012; **69**(5): 476-483. doi: http://dx.doi.org/10.1001/archgenpsychiatry.2011.1532
10. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*. 2000; **321**(7273): 1371-1376. doi: http://dx.doi.org/10.1136/bmj.321.7273.1371
11. de Haan L, Lavalaye J, van Bruggen M, van Nimwegen L, Booij J, van Amelsvoort T, et al. Subjective experience and dopamine D2 receptor occupancy in patients treated with antipsychotics: clinical implications. *Can J Psychiatry*. 2004; **49**(5): 290– 296
12. Price R, Salavati B, Graff-Guerrero A, Blumberger DM, Mulsant BH, Daskalakis ZJ, et al. Effects of antipsychotic D2 antagonists on long-term potentiation in animals and implications for human studies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014**; 54**: 83-91. doi: http://dx.doi.org/10.1016/j.pnpbp.2014.05.001

(received, 2015-08-12; accepted, 2015-08-20)

In 1997 Professor Chuanyue Wang obtained his doctor’s degree from the Mental Health Research Institute, Xiangya School of Medicine, Central South University. He is currently the director of the Department of Adult Psychiatry at Beijing Anding Hospital and a professor at Capital Medical University. His main research interests are pharmacotherapeutics and bio markers of psychiatric disorders.