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ORIGINAL ARTICLE

# Concurrent antipsychotic use in older adults treated with antidepressants in Asia

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## Abstract

**Aim:** Depressive disorders are common in old age. Antipsychotics (APs) are often used as an adjunctive treatment with antidepressants (ADs) in this population but its patterns of use in Asia are not known. This study explored the rate of combination of APs and ADs in older adult psychiatric patients in Asia.

**Methods:** This is a secondary analysis of the database of a multicentre study which recorded participants' basic demographical and clinical data in standardised format in 10 Asian countries and territories. The data were analysed using univariate and multivariate logistic regression analyses.

**Results:** A total of 955 older adult psychiatric in- and outpatients were included in this study. The proportion of concurrent AP and AD use was 32.0%, ranging from 23.3% in Korea to 44.0% in Taiwan. Multivariate logistic regression analysis found that younger age, inpatient status and diagnosis of schizophrenia, anxiety and other mental disorders were significantly related to a higher proportion of concurrent use of APs and ADs.

**Conclusion:** Around a third of older adult psychiatric patients had concurrent AP and AD use in the Asian countries/regions surveyed. Considering the uncertain effectiveness and questionable safety of the AP and AD combination in this patient population, such should be cautiously used.

 

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## INTRODUCTION

Depressive disorders are frequent in older adults. For example, one survey found that the prevalence of major depression was up to 16% in old people living in private households or institutions.[1] Another study reported that the prevalence of major depressive disorder, minor depression and clinically relevant depressive symptoms in old people living in the community were 1.8%, 9.8% and 13.5%, respectively.[2] Compared to younger adults, older adults suffering from depression have an increased risk of physical and psychological comorbidities, more disability and social isolation,[3–6] greater economic cost,[7,8] and higher mortality.[1,9]

Psychotropic medications are prescribed for older adults up to 7–18 times more frequently than for middle-aged adults.[10] Of the psychotropic medications, antidepressants (ADs) are one of those most widely prescribed.[11,12] For example, one study found that 51.8% of nursing home residents suffered from depression, of whom 82.8% received ADs.[13] Antipsychotics (APs), such as aripiprazole, quetiapine and olanzapine, are often used for augmenting ADs for depression.[14] Over half of older adults who received ADs are also prescribed other psychotropic drugs, particularly benzodiazepines (BZDs) and APs.[15] Compared to younger adults, due to their poorer general health status and age-related physiological changes, older adults are more likely to experience medication-induced adverse events.[16,17] Therefore, polypharmacy using psychotropic medications in older adults, if indicated at all, should be cautiously prescribed.

Regular surveys of prescription patterns are useful to examine the appropriateness of pharmacotherapy.[18] Although AP and AD combinations are often used, the frequency of such co-prescription patterns are unknown in older adult psychiatric patients in Asia. This study set out to examine the concurrent use of APs and ADs in older adult psychiatric patients in several Asian countries and territories, and explore its independent demographic and clinical correlates.

## METHODS

### Study design and sample

The Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) project is an international, multicentre survey on the use of ADs,[19] which was conducted between March and June 2013 in 42 centres and hospitals in 10 Asian territories and countries, including China, Malaysia, Hong Kong, India, Indonesia, Japan, Thailand, Korea, Singapore and Taiwan. Patients with any mental disorder treated with ADs on the day of data collection were consecutively screened and enrolled in the

 

survey. The data were collected with a standardised protocol in all participating hospitals. Patients who were eligible for the study were aged 50 years or above and were either in- or outpatients. In many Asian countries, patients aged 50 years or older are defined as 'older adult'. This cut-off is in line with some other studies.[20–22] The study protocol was approved by the Institutional Review Boards at each participating centre and hospital. When the survey involved retrospective anonymous medical chart review, informed consent was waived. However, when patients were interviewed, they provided written informed consent.

### Assessment

Patients' demographical and clinical data were retrieved by reviewing medical records, or during a clinical interview supplemented by a review of medical records. Diagnoses were established according to *International Classification of Diseases*, 10th revision[23] or *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.[24] For the sake of comparison in the statistical analysis, doses of ADs were transformed into imipramine equivalent (IMI-eq) doses.[25]

### Statistics

Data analyses were performed with the SPSS statistical package, Version 20 (SPSS Inc., Chicago, IL, USA). The demographical and clinical data were compared between patients treated with APs plus ADs and on ADs only with Mann–Whitney *U*-test, independent samples *t*-test or $\chi^2$ test, if applicable. Independent associations between demographical and clinical characteristics (independent variables) and the combination of APs and ADs (dependent variable) were explored with binary logistic regression analysis. The variables that significantly differed in univariate analysis were entered as independent variables, and the combination of APs and ADs was the dependent variable. Statistical significance was set at 0.05 (two-sided).

## RESULTS

A total of 955 older adult patients who received antidepressants were enrolled in the study. The rate of combination of APs and ADs in the whole sample was 32.0% ranging from 23.3% in Korea to 44.0% in Taiwan (Table 1). Table 2 shows the demographic

**Table 1** Prescription of psychotropic medications for older adult psychiatric patients by country/territory

| | China (*N* = 158) | | Hong Kong (*N* = 39) | | Japan (*N* = 119) | | RO Korea (*N* = 150) | | Singapore (*N* = 48) | | Taiwan (*N* = 109) | | India (*N* = 63) | | Malaysia (*N* = 67) | | Thailand (*N* = 128) | | Indonesia (*N* = 74) | | Overall (*N* = 955) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Country/territory | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| APs | 51 | 32.3 | 17 | 43.6 | 40 | 33.6 | 35 | 23.3 | 17 | 35.4 | 48 | 44.0 | 16 | 25.4 | 20 | 29.9 | 30 | 23.4 | 32 | 43.2 | 306 | 32.0 |
| TCAs | 6 | 3.8 | 3 | 7.7 | 15 | 12.6 | 18 | 12 | 1 | 2.1 | 8 | 7.3 | 7 | 11.1 | 1 | 1.5 | 33 | 25.8 | 7 | 9.5 | 99 | 10.4 |
| Tetracyclics | 0 | 0 | 0 | 0 | 7 | 5.9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1.5 | 19 | 14.8 | 0 | 0 | 27 | 2.8 |
| SSRIs | 103 | 65.2 | 21 | 53.8 | 52 | 43.7 | 101 | 67.3 | 30 | 62.5 | 57 | 52.3 | 44 | 69.8 | 47 | 70.1 | 71 | 55.5 | 67 | 90.5 | 593 | 62.1 |
| SNRIs | 42 | 26.6 | 7 | 17.9 | 24 | 20.2 | 35 | 23.3 | 3 | 6.3 | 22 | 20.2 | 10 | 15.9 | 4 | 6 | 8 | 6.3 | 0 | 0 | 155 | 16.2 |
| NaSSAs | 31 | 19.6 | 6 | 15.4 | 40 | 33.6 | 36 | 24 | 12 | 25 | 11 | 10.1 | 6 | 9.5 | 13 | 19.4 | 8 | 6.3 | 0 | 0 | 163 | 17.1 |
| Other drugs | 12 | 7.6 | 6 | 15.4 | 16 | 13.4 | 39 | 26 | 5 | 10.4 | 23 | 21.1 | 2 | 3.2 | 2 | 3 | 22 | 17.2 | 0 | 0 | 127 | 13.3 |
| BZDs | 64 | 40.5 | 19 | 48.7 | 71 | 59.7 | 40 | 26.7 | 16 | 33.3 | 76 | 69.7 | 18 | 28.6 | 31 | 46.3 | 50 | 39.1 | 38 | 51.4 | 423 | 44.3 |
| MS | 5 | 3.2 | 1 | 2.6 | 15 | 12.6 | 5 | 3.3 | 4 | 8.3 | 11 | 10.1 | 6 | 9.5 | 0 | 0.0 | 12 | 9.4 | 4 | 5.4 | 63 | 6.6 |

AP, antipsychotic; BZD, benzodiazepine; MS, mood stabilizer; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin/norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

**Table 2** Basic demographic and clinical characteristics of the study sample

| | Whole sample (*N* = 955) | | No APs (*n* = 649) | | On APs (*n* = 306) | | Statistics | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | *t* /*z* | *df* | *P* |
| Age (years) | 62.6 | 9.5 | 63.3 | 9.7 | 60.9 | 8.7 | 3.7 | 953 | **<0.001** |
| AD dose, IMIeq (mg/day) | 131.2 | 112.5 | 126.5 | 109.1 | 141.1 | 118.8 | −1.9 | --- | 0.051 |
| Number of ADs | 1.2 | 0.5 | 1.27 | 0.51 | 1.21 | 0.53 | −2.1 | --- | **0.029** |
| Number of depressive symptoms | 3.4 | 2.0 | 3.4 | 2.0 | 3.5 | 2.1 | −0.8 | --- | 0.38 |
| | *n* | % | *n* | % | *n* | % | $\chi^2$ | *df* | *P* |
| Age (years) | | | | | | | 9.1 | 1 | **0.002** |
| 50–64 | 615 | 64.4 | 397 | 61.2 | 218 | 71.2 | | | |
| 65 and older | 340 | 35.6 | 252 | 38.8 | 88 | 28.8 | | | |
| Male | 375 | 39.3 | 238 | 36.7 | 137 | 44.8 | 5.7 | 1 | **0.017** |
| Psychiatric hospital | 351 | 36.8 | 201 | 31.0 | 150 | 49.0 | 29.1 | 1 | **<0.001** |
| Outpatients | 722 | 75.6 | 544 | 83.8 | 178 | 58.2 | 74.1 | 1 | **<0.001** |
| General hospital psychiatric unit | 687 | 71.9 | 448 | 69.0 | 239 | 78.1 | 8.4 | 1 | **0.004** |
| Country/territory | | | | | | | 25.2 | 9 | **0.003** |
| Income | | | | | | | 3.1 | 2 | 0.21 |
| High income | 465 | 48.7 | 308 | 47.5 | 157 | 51.3 | | | |
| Upper middle income | 353 | 37.0 | 252 | 38.8 | 101 | 33.0 | | | |
| Lower middle income | 137 | 14.3 | 89 | 13.7 | 48 | 15.7 | | | |
| Major medical conditions | 421 | 44.1 | 281 | 43.3 | 140 | 45.8 | 0.5 | 1 | 0.47 |
| Use of antidepressants | | | | | | | | | |
| TCAs | 99 | 10.4 | 75 | 11.6 | 24 | 7.8 | 3.0 | 1 | 0.07 |
| Tetracyclics | 27 | 2.8 | 21 | 3.2 | 6 | 2.0 | 1.2 | 1 | 0.26 |
| SSRIs | 593 | 62.1 | 407 | 62.7 | 186 | 60.8 | 0.3 | 1 | 0.56 |
| SNRIs | 155 | 16.2 | 104 | 16.0 | 51 | 16.7 | 0.06 | 1 | 0.80 |
| NaSSAs | 163 | 17.1 | 109 | 16.8 | 54 | 17.6 | 0.1 | 1 | 0.74 |
| Other ADs | 127 | 13.3 | 85 | 13.1 | 42 | 13.7 | 0.07 | 1 | 0.79 |
| Use of MS | 63 | 6.6 | 31 | 4.8 | 32 | 10.5 | 10.8 | 1 | **0.001** |
| Use of BZDs | 423 | 44.3 | 268 | 41.3 | 155 | 50.7 | 7.3 | 1 | **0.007** |
| Principal psychiatric diagnosis | | | | | | | 93.5 | 3 | **<0.001** |
| Mood disorders | 671 | 70.3 | 479 | 73.8 | 192 | 62.7 | | | |
| Anxiety disorders | 130 | 13.6 | 109 | 16.8 | 21 | 6.9 | | | |
| Schizophrenia | 79 | 8.3 | 19 | 2.9 | 60 | 19.6 | | | |
| Other diagnoses | 75 | 7.9 | 42 | 6.5 | 33 | 10.8 | | | |

Bolded values: <0.05. AD, antidepressant; AP, antipsychotic; BZD, benzodiazepine; IMI-eq, imipramine-equivalent; MS, mood stabilizer; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin/norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.

and clinical data for the whole sample and separately for the ADs and the combination groups. In the whole sample, the mean age was 62.6 years and 375 patients (39.3%) were men; the proportion of mood disorders, anxiety disorders, schizophrenia and other diagnoses was 70.3%, 13.6%, 8.3% and 7.9%, respectively. The mean dose of ADs in IMI-eq was 131.2 mg/day.

Concurrent APs and ADs use was significantly associated with younger age, male gender, lower numbers of ADs, inpatient treatment, in psychiatric or public hospitals, more frequent use of mood stabilisers (MS) and BZDs, and psychiatric diagnoses (Table 2). Binary logistic regression analyses found that concurrent APs abd ADs prescriptions were independently related to younger age, inpatient treatment and diagnosis of schizophrenia, anxiety and other mental disorders (Table 3).

## DISCUSSION

This was the first survey of concurrent use of APs and ADs in older adult psychiatric patients in Asia. The proportion of concurrent prescriptions was 32.0% in the whole sample but it varied markedly across countries/territories, with the highest in Taiwan (44.0%) and lowest in Korea (23.3%). These figures are much higher than the corresponding ones in the USA (13.9%) and Europe (12.3%).[26] The discrepancy across study sites could be related to the

**Table 3** Independent demographic and clinical correlates of concurrent antipsychotic and antidepressant use

| Variables | *P*-value | Odds ratio | 95% CI |
|---|---|---|---|
| Age (years) | **0.026** | 0.98 | 0.963–0.998 |
| Number of ADs | 0.97 | 1.006 | 0.727–1.392 |
| Male | 0.301 | 0.181 | 0.861–1.619 |
| Psychiatric hospital | 0.424 | 1.183 | 0.783–1.787 |
| Outpatients | **<0.001** | 0.305 | 0.213–0.438 |
| General hospital psychiatric unit | 0.307 | 1.309 | 0.781–2.192 |
| Use of MS | 0.253 | 1.41 | 0.783–2.539 |
| Use of BZDs | 0.519 | 1.112 | 0.806–1.533 |
| Principal psychiatric diagnosis | | | |
| Mood disorders | — | 1 | — |
| Anxiety disorders | **0.01** | 0.493 | 0.289–0.842 |
| Schizophrenia | **<0.001** | 6.284 | 3.432–11 505 |
| Other diagnoses | **0.004** | 2.265 | 1.296–3.957 |
| Country/territory | | | |
| China | 0.395 | 1 | 0 |
| Hong Kong | 0.271 | 1.586 | 0.698–3.606 |
| Japan | 0.276 | 1.408 | 0.761–2.609 |
| South Korea | 0.554 | 1.238 | 0.611–2.509 |
| Singapore | 0.951 | 1.028 | 0.429–2.463 |
| Taiwan | 0.367 | 1.360 | 0.698–2.651 |
| India | 0.325 | 1.456 | 0.689–3.075 |
| Malaysia | 0.541 | 1.265 | 0.596–2.688 |
| Thailand | 0.391 | 0.765 | 0.415–1.411 |
| Indonesia | **0.039** | 2.004 | 1.035–3.878 |

Bold values: <0.05; participating country/territory has been controlled for as a covariate. AD, antidepressants; BZD, benzodiazepine; MS, mood stabilizer

diversity of socio-cultural factors, local clinical practices, healthcare polices, medication cost, and insurance coverage.[27] For example, there is a widely held view in Asia that combination of medications of different pharmacological activities has better efficacy in clinical practice.[28] In addition, the co-existence of psychotic and depressive symptoms occurring in various psychiatric disorders are frequent in elderly patients, increasing the likelihood of concurrent use of APs and ADs. As the risk of side effects of psychotropic drugs may increase due to the age-related changes in pharmacokinetic and pharmacodynamic responses in older patients,[17] the safety of APs and ADs combinations should be taken into consideration in clinical practice.

Concurrent use of APs and ADs was associated with psychiatric diagnoses (particularly schizophrenia), younger age and inpatient treatment in this study. ADs were often prescribed for negative and depressive symptoms and cognitive impairment in schizophrenia.[29] Negative and depressive symptoms could be improved in around a third of schizophrenia patients receiving ADs[30,31] and adjunctive ADs.[32–34] This may be related to the effect of ADs in modifying serotonergic (5-HT) dysfunction that is thought to be involved in the pathophysiology of psychotic symptoms.[14,35,36]

Although AD monotherapy has been recommended in treating depressive disorders,[37] adjunctive APs are often used as an augmentation strategy for treatment-resistant depression.[38] Second generation antipsychotics (SGAs) are frequently co-prescribed with ADs[39,40] given that SGAs improve depressive symptoms[41] by enhancing monoaminergic transmission.[14,42] A meta-analysis demonstrated that adjunctive SGAs have significant effects on the severity of major depression, resulting in improved quality of life and less functional deficit.[43]

In this survey, inpatients were more likely to be treated with APs and ADs combinations, probably due to the more severe psychiatric symptoms.[44] Previous studies in the USA and Europe found that depressed patients prescribed with APs present with more severe comorbid psychotic symptoms.[26] The finding that younger age was associated with concurrent APs and ADs use is perhaps due to the better tolerance of polypharmacy in younger ages. Conversely, the higher risk of medication-induced adverse events in older patients may discourage psychiatrists to prescribe combinations of psychotropic medications.

Several limitations of the study should be acknowledged. First, the sample size in several countries/territories was small, therefore analyses could not be performed separately in each study site. Second, as only 10 Asian countries/territories were included in the study, the findings are not representative of the whole Asian patient population. Third, due to the cross-sectional study the causality between variables could not be explored. Fourth, due to logistical reasons the severity of depressive and psychotic symptoms was not measured, hence their associations with prescription patterns could not be analyzed. Fifth, the study mainly focused on prescription of ADs in psychiatric hospitals or psychiatric units in general hospitals. Patients with other psychiatric and medical diagnoses treated with ADs, such as dementia or other neuropsychiatric disorders, are rarely treated in psychiatric hospitals/units in most Asian countries, thus they were not covered in this study. Finally, several relevant factors of prescription patterns, such as cost of treatment, were not recorded.

In conclusion, around a third of older adult psychiatric patients in 10 Asian countries and territories received concurrent ADs and APs. Given the increased age-related risks of psychotropic medication-induced side effects, the combination of ADs and APs should be used with caution in this population.

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## REFERENCES

1 Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. *Acta Psychiatr Scand* 2006; **113**: 372–387.
2 Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry* 1999; **174**: 307–311.
3 Valkanova V, Ebmeier KP. Vascular risk factors and depression in later life: a systematic review and meta-analysis. *Biol Psychiatry* 2013; **73**: 406–413.
4 Gansler DA, Suvak M, Arean P, Alexopoulos GS. Role of executive dysfunction and dysexecutive behavior in late-life depression and disability. *Am J Geriatr Psychiatry* 2015; **23**: 1038–1045.
5 Grossberg GT, Beck D, Zaidi SNY. Rapid depression assessment in geriatric patients. *Clin Geriatr Med* 2017; **33**: 383–391.
6 Fiske A, Wetherell JL, Gatz M. Depression in older adults. *Annual Rev Clin Psychol* 2009; **5**: 363–389.
7 Luppa M, Heinrich S, Matschinger H *et al*. Direct costs associated with depression in old age in Germany. *J Affect Disord* 2008; **105**: 195–204.
8 Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci* 2003; **58**: M249–M265.
9 Wilson K, Mottram PG, Sivananthan A, Nightingale A. Antidepressants versus placebo for the depressed elderly. *Cochrane Database of Systematic Review* 2001; **2**: CD000561.
10 Voyer P, Martin LS. Improving geriatric mental health nursing care: making a case for going beyond psychotropic medications. *Int JMental Health Nursing* 2003; **12**: 11–21.
11 Aarts N, Noordam R, Hofman A, Tiemeier H, Stricker BH, Visser LE. Utilization patterns of antidepressants between 1991 and 2011 in a population-based cohort of middle-aged and elderly. *Eur Psychiatry* 2014; **29**: 365–370.
12 Parabiaghi A, Franchi C, Tettamanti M *et al*. Antidepressants utilization among elderly in Lombardy from 2000 to 2007: dispensing trends and appropriateness. *Eur J Clin Pharmacol* 2011; **67**: 1077–1083.
13 Gaboda D, Lucas J, Siegel M, Kalay E, Crystal S. No longer undertreated? Depression diagnosis and antidepressant therapy in elderly long-stay nursing home residents, 1999 to 2007. *J Am Geriatr Soc* 2011; **59**: 673–680.
14 Han C, Wang S-M, Kato M *et al*. Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. *Expert Rev Neurother* 2013; **13**: 851–870.
15 Fulone I, Lopes LC. Potentially inappropriate prescriptions for elderly people taking antidepressant: comparative tools. *BMC Geriatr* 2017; **17**: 278.
16 Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; **57**: 6–14.
17 Uchida H, Mamo DC, Mulsant BH, Pollock BG, Kapur S. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. *The J Clin Psychiatry* 2009; **70**: 397–405.
18 Ungvari GS, Chow LY, Chiu HF, Ng FS, Leung T. Modifying psychotropic drug prescription patterns: a follow-up survey. *Psychiatry Clin Neurosci* 1997; **51**: 309–314.
19 Zhong XM, Wang F, Zhang Q *et al*. Concurrent benzodiazepine use in older adults treated with antidepressants in Asia. *Int Psychogeriatr* 2017: 1–7. doi: 10.1017/S1041610217002563.
20 Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* 2003; **160**: 1147–1156.
21 Dassori AM, Copeland LA, Zeber JE, Miller AL. Factors in second-generation antipsychotic switching patterns in a national sample of older veterans with schizophrenia. *Psychiatr Serv* 2011; **62**: 47–53.
22 Duberstein PR, Conwell Y, Seidlitz L, Denning DG, Cox C, Caine ED. Personality traits and suicidal behavior and ideation in depressed inpatients 50 years of age and older. *J Gerontology B* 2000; **55**: P18–P26.
23 WHO. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization, 1992. Inadequate details.
24 APA. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington: American Psychiatric Association, 1994.
25 Rajaratnam K, Xiang YT, Tripathi A *et al*. Factors associated with antidepressant dosing in Asia: findings from the Research on Asian Psychotropic Prescription Study. *J Clin Psychopharmacol* 2016; **36**: 716–719.
26 McIntyre RS, Weiller E. Real-world determinants of adjunctive antipsychotic prescribing for patients with major depressive disorder and inadequate response to antidepressants: a case review study. *Adv Ther* 2015; **32**: 429–444.
27 Xiang YT, Ungvari GS, Wang CY *et al*. Adjunctive antidepressant prescriptions for hospitalized patients with schizophrenia in Asia (2001–2009). *Asia Pac Psychiatry* 2013; **5**: E81–E87. https://doi.org/10.1111/j.1758-5872.2012.00231.x.
28 Phillips MR, Lu SH, Wang RW. Economic reforms and the acute inpatient care of patients with schizophrenia: the Chinese experience. *Am J Psychiatry* 1997; **154**: 1228–1234.
29 Mao Y-M, Zhang M-D. Augmentation with antidepressants in schizophrenia treatment: benefit or risk. *Neuropsychiatr Dis Treat* 2015; **11**: 701.
30 Himelhoch S, Slade E, Kreyenbuhl J, Medoff D, Brown C, Dixon L. Antidepressant prescribing patterns among VA patients with schizophrenia. *Schizophr Res* 2012; **136**: 32–35.
31 Acquaviva E, Gasquet I, Falissard B. Psychotropic combination in schizophrenia. *Eur J Clin Pharmacol* 2005; **61**: 855–861.
32 Galling B, Vernon JA, Pagsberg AK *et al*. Efficacy and safety of antidepressant augmentation of continued antipsychotic treatment in patients with schizophrenia. *Acta Psychiatr Scand* 2018; **137**: 187–205.
33 Helfer B, Samara MT, Huhn M *et al*. Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a

systematic review and meta-analysis. *Am J Psychiatry* 2016; **173**: 876–886.
34 Rummel C, Kissling W, Leucht S. Antidepressants for the negative symptoms of schizophrenia. *Cochrane Database Syst Rev* 2006; **3**: Cd005581.
35 Meltzer HY. Serotonergic mechanisms as targets for existing and novel antipsychotics. *Handb Exp Pharmacol* 2012; **212**: 87–124.
36 Meltzer H, Massey B. The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr Opin Pharmacol* 2011; **11**: 59–67.
37 Cosgrove L, Shaughnessy AF, Peters SM, Lexchin JR, Bursztajn H, Bero L. Conflicts of interest and the presence of methodologists on guideline development panels: a cross-sectional study of clinical practice guidelines for major depressive disorder. *Psychother Psychosom* 2017; **86**: 168–170.
38 Dold M, Kasper S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression. *Int J Psychiatry Clin Practice* 2017; **21**: 13–23.
39 Berman RM, Fava M, Thase ME *et al*. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr* 2009; **14**: 197–206.
40 Marcus RN, McQuade RD, Carson WH *et al*. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2008; **28**: 156–165.
41 Rogoz Z. Combined treatment with atypical antipsychotics and antidepressants in treatment-resistant depression: preclinical and clinical efficacy. *Pharmacol Rep* 2013; **65**: 1535–1544.
42 Blier P. Rational site-directed pharmacotherapy for major depressive disorder. *Int J Neuropsychopharmacol* 2014; **17**: 997–1008.
43 Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med* 2013; **10**: e1001403.
44 Möller H-J, Seemüller F, Schennach-Wolff R, Stübner S, Rüther E, Grohmann R. History, background, concepts and current use of comedication and polypharmacy in psychiatry. *Int J Neuropsychopharmacol* 2014; **17**: 983–996.

 