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ORIGINAL RESEARCH

Dilemma of prescribing aripiprazole under the Taiwan health insurance program: a descriptive study

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Objectives: Refractory major depressive disorder (MDD) is a serious problem leading to a heavy economic burden. Antipsychotic augmentation treatment with aripiprazole and quetiapine is approved for MDD patients and can achieve a high remission rate. This study aimed to examine how psychiatrists in Taiwan choose medications and how that choice is influenced by health insurance payments and administrative policy.

Design: Descriptive study.

Outcome measures: Eight questions about the choice of treatment strategy and atypical antipsychotics, and the reason to choose aripiprazole.

Intervention: We designed an augmentation strategy questionnaire for psychiatrists whose patients had a poor response to antidepressants, and handed it out during the annual meeting of the Taiwanese Society of Psychiatry in October 2012. It included eight questions addressing the choice of treatment strategy and atypical antipsychotics, and the reason whether or not to choose aripiprazole as the augmentation antipsychotic.

Results: Choosing antipsychotic augmentation therapy or switching to other antidepressant strategies for MDD patients with an inadequate response to antidepressants was common with a similar probability (76.1% vs 76.4%). The most frequently used antipsychotics were aripiprazole and quetiapine, however a substantial number of psychiatrists chose olanzapine, risperidone, and sulpiride. The major reason for not choosing aripiprazole was cost (52.1%), followed by insurance official policy audit and deletion in the claims review system (30.1%).

Conclusion: The prescribing behavior of Taiwanese psychiatrists for augmentation antipsychotics is affected by health insurance policy.

Keywords: major depressive disorder, aripiprazole, psychiatrists, prescribing behavior, antipsychotic augmentation, National Health Insurance program

Introduction

Major depressive disorder (MDD) is a common and recurrent mental illness with a lifetime prevalence of 5%–12% in adult men and 9%–26% in adult women. In spite of recent advances in psychopharmacology, approximately 60% of patients with MDD do not achieve an adequate response or remission to initial antidepressant therapy (ADT) even with adequate dose and duration.[1]

Common strategies adopted for nonresponders to ADT include switching to other antidepressants, combining therapy with antidepressants of another class, and augmentation strategies with atypical antipsychotics, lithium, or thyroid hormone.[2–4] The United States Food and Drug Administration (FDA) has approved aripiprazole and quetiapine as adjunctive treatment for MDD,[5] however few studies have been

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conducted on the actual choices of psychiatrists for nonresponders to ADT.

The prescribing behavior of physicians is influenced by many factors, including evidence-based medical knowledge, training and continuous education, and largely by health insurance and reimbursement or payment policies.[6–8] The aim of this study was to examine how Taiwanese psychiatrists prescribe medication and how they are influenced by health insurance payments and administrative policy.

Methods

This descriptive study used an innovative questionnaire for Taiwanese psychiatrists on augmentation strategy for MDD patients with an inadequate response to ADT. The aim of this questionnaire was to examine the influence of health insurance payments and administrative policy on the prescribing behavior of Taiwanese psychiatrists. The first question asked how many MDD outpatients per month each Taiwanese psychiatrists treated. The second question asked about the percentage of poor responders to ADT, and the third question asked about the remission rate of MDD. The fourth question asked about the strategies used for the poor responders to ADT, and the fifth question asked which antipsychotics were chosen for antipsychotic augmentation therapy. The sixth and seventh questions asked why and why not aripiprazole was chosen as the augmentation antipsychotic. The eighth question asked why augmentation antipsychotics were not chosen. We handed out the questionnaire during the annual meeting of the Taiwanese Society of Psychiatry in October 2012.

Statistical analysis

Outpatient visits per month, percentage of poor responders to ADT, remission rate, the strategies used for the poor responders to ADT, and choice of augmentation antipsychotics were presented with numbers and percentages. The answers to questions 4–8 according to the number of MDD outpatients per month were compared using chi-square and Fisher's exact tests. Analysis of covariance (ANCOVA) was used to analyze the relationship between the answers to questions 4–8 and the number of MDD outpatients per month after including poor response proportion and remission rate as covariates. Multiple logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the correlate variables associated with aripiprazole and quetiapine. The IBM SPSS Statistics version 22 (IBM® SPSS® Statistics 22, IBM, New York, NY, USA) was used for statistical analysis, and the significance level (*P*-value) was set at 0.05.

Results

We collected 324 questionnaires with complete data. The most common strategies for treating MDD patients with an inadequate response to ADT were switching to antidepressants with different mechanisms (76.4%), augmentation with antipsychotics (76.1%), combination with other antidepressants (35.4%), and electroconvulsive therapy (14.6%) (Table 1).

The antipsychotics used for MDD were aripiprazole (78.2%), quetiapine (62%), olanzapine (34.6%), risperidone (30.2%), and sulpiride (27.4%). The reasons psychiatrists chose aripiprazole for augmentation included fewer adverse effects (72.5%), good response (59.7%), FDA indication (55.6%), and rapid onset of action (33.4%). The psychiatrists who chose not to prescribe aripiprazole as the augmentation antipsychotic did so because of price (52.1%), official insurance policy audit and deletion of payments (30.8%), adverse effects (29.2%), response (12.7%), and not knowing enough about the drug (8.3%). Concerns when considering augmentation antipsychotics were insurance audit and deletion (53%), price (36.6%), side effects (35%), response (12%), and not knowing enough about the drug (1.9%) (Table 1).

The data in Table 2 reveals several statistical differences among groups of those who treated different numbers of MDD patients per month (<100, 101–200, and >200), in the antipsychotics chosen, the reasons why they did not choose aripiprazole, and the reasons why they did not choose antipsychotics for augmentation. For example, the reason why psychiatrists in the group of 101–200 treated patients/month, chose not to augment with antipsychotics due to "health insurance payment audit and deletion", is significantly higher than other groups (76 in 129, 59.4%, $P<0.001$ in ANCOVA) (Table 2).

In further analysis by the number of patients the psychiatrists treated per month, those who saw 101–200 persons/month were more likely to choose quetiapine and olanzapine as augmentation strategy, but those who saw more than 200 persons/month were less likely to choose quetiapine and olanzapine as augmentation strategy. There was no difference in choosing aripiprazole as the augmentation strategy between the groups (Table 3).

Discussion

Treatment-resistant depression is associated with extensive use of general and psychiatric medical services, which poses

Table 1 Questionnaire for Taiwanese psychiatrists on MDD patients with a poor response to ADT

Question	Category	Number (n=324)	Percent (%)
1. How many outpatients with major depressive disorder do you treat per month?	Below 50 persons	62	19.1
	50–100 persons	92	28.4
	101–150 persons	69	21.3
	151–200 persons	60	18.5
	More than 200 persons	41	12.7
2. What proportion of your MDD patients have a poor response to antidepressant therapy?	Below 10%	7	2.2
	10%–20%	76	23.7
	20%–30%	158	49.2
	30%–40%	60	18.7
	Above 40%	20	6.2
3. What is the remission rate of MDD patients with antidepressant therapy?	Below 50%	52	16.3
	50%–60%	128	40.1
	60%–70%	69	21.6
	70%–80%	61	19.1
	Above 80%	9	2.8
4. How will you treat patients with a poor response to antidepressant therapy? (multiple choices)	Switch to other antidepressants with different mechanism	246	76.4
	Augmentation antipsychotics	245	76.1
	Combination with other antidepressants	114	35.4
	ECT	47	14.6
	Others	9	2.8
5. Which antipsychotics do you often prescribe? (multiple choices)	Aripiprazole	251	78.2
	Olanzapine	111	34.6
	Quetiapine	199	62.0
	Risperidone	97	30.2
	Sulpiride	88	27.4
	Others	7	2.2
6. Why did you choose aripiprazole? (multiple choices)	Good effect	191	59.7
	Rapid onset	107	33.4
	Few adverse effects	232	72.5
	Cheap price	13	4.1
	FDA indication	178	55.6
	Others	2	0.6
7. Why did you not choose aripiprazole? (multiple choices)	Effect	40	12.7
	Adverse effects	92	29.2
	Price	164	52.1
	Not knowing enough about the drug	26	8.3
	Health insurance payment audit and deletion	97	30.8
	Others	12	3.8
8. Why did you not choose augmentation antipsychotics? (multiple choices)	Effect	38	12.0
	Adverse effects	111	35.0
	Price	116	36.6
	Not knowing enough about the drug	6	1.9
	Health insurance audit and deletion	168	53.0
	Others	32	10.1

Abbreviations: ADT, antidepressant therapy; ECT, electroconvulsive therapy; MDD, major depressive disorder; FDA, US Food and Drug Administration.

substantial economic burden and work loss costs.[9,10] The prescribing behavior of psychiatrists may influence the outcomes of refractory MDD and cause a delay in the use of adequate antipsychotic augmentation therapy. It is important therefore for health policy makers to understand the prescribing behaviors and modify the insurance policy accordingly.

The national health care system in Taiwan, known as the National Health Insurance (NHI) program, was instituted in 1995. The NHI program is a single-payer compulsory social insurance plan which centralizes the disbursement of health care funds.[11,12] The system promises equal access to health care for all citizens, and the population coverage had reached

Table 2 Analysis of medication selection according to the number of MDD outpatients per month

Question	Category	Number of MDD outpatients per month			*P*-value[a,b]	*P*-value[c]
		Below 100 persons	101–200 persons	Above 200 persons		
		n (%)	n (%)	n (%)		
4. How will you treat patients with a poor response to antidepressant therapy? (multiple choices)	Switch to other antidepressants with different mechanisms	107 (69.9)	109 (84.5)	30 (75.0)	0.016	0.038
	Augmentation antipsychotics	111 (72.5)	99 (76.7)	35 (87.5)	0.139	0.255
	Combination with other antidepressants	47 (30.7)	52 (40.3)	15 (37.5)	0.234	0.208
	ECT	25 (16.3)	19 (14.7)	3 (7.5)	0.37	0.079
	Total (n=322)	153 (100.0)	129 (100.0)	40 (100.0)		
5. Which antipsychotics do you often prescribe? (multiple choices)	Aripiprazole	118 (77.6)	99 (76.7)	34 (85)	0.529	0.722
	Olanzapine	53 (34.9)	53 (41.1)	5 (12.5)	0.004	0.004
	Quetiapine	85 (55.9)	97 (75.2)	17 (42.5)	<0.001	<0.001
	Risperidone	59 (38.8)	29 (22.5)	9 (22.5)	0.006	0.007
	Sulpiride	38 (25)	42 (32.6)	8 (20.0)	0.195	0.221
	Total (n=321)	152 (100.0)	129 (100.0)	40 (100.0)		
6. Why did you choose aripiprazole? (multiple choices)	Good effect	88 (58.3)	77 (60.2)	26 (63.4)	0.83	0.586
	Rapid onset	49 (32.5)	40 (31.2)	18 (43.9)	0.307	0.077
	Few adverse effects	103 (68.2)	97 (75.8)	32 (78.0)	0.257	0.421
	Cheap price	7 (4.6)	4 (3.1)	2 (4.9)	0.784	0.665
	FDA indication	74 (49)	76 (59.4)	28 (68.3)	0.048	0.137
	Total (n=320)	151 (100.0)	128 (100.0)	41 (100.0)		
7. Why did you not choose aripiprazole? (multiple choices)	Drug effect	26 (17.7)	12 (9.4)	2 (5)	0.035	0.157
	Adverse effects	39 (26.5)	34 (26.6)	19 (47.5)	0.025	0.042
	Price	64 (43.5)	80 (62.5)	20 (50.0)	0.007	0.007
	Not knowing associated information	23 (15.6)	3 (2.3)	0 (0)	<0.001[b]	<0.001
	Health insurance payment audit and deletion	48 (32.71)	39 (30.5)	10 (25.0)	0.646	0.200
	Total (n=315)	147 (100.0)	128 (100.0)	40 (100.0)		
8. Why did you not choose augmentation antipsychotic? (multiple choices)	Drug effect	16 (10.8)	17 (13.3)	5 (12.2)	0.819	0.620
	Adverse effects	44 (29.7)	53 (41.4)	14 (34.1)	0.127	0.036

Price	42 (28.4)	60 (46.9)	14 (34.1)	0.006	0.022	
Not knowing associated information	3 (2)	3 (2.3)	0 (0)	0.623	0.785	
Health insurance payment audit and deletion	79 (53.4)	76 (59.4)	13 (31.7)	0.008	<0.001	
Total (n=317)	148 (100.0)	128 (100.0)	41 (100.0)			

Notes: [a]Chi-square test, [b]Fisher's exact test, [c]Analysis of covariance (after including poor response proportion and remission rate as covariates). As some psychiatrists missed questions, the column totals do not equal the total number.
Abbreviations: ECT, electroconvulsive therapy; FDA, US Food and Drug Administration.

99% by the end of 2004.[13,14] Although patient satisfaction with the NHI program was reported to be more than 80% in 2011,[15] doctors have reported dissatisfaction because of instability in NHI regulations, a complicated medical claims system, and excessive working hours.[16] Doctors can be heavily penalized for a wide variety of reasons such as seeing too many patients or offering too many services even if they were appropriate under a budget-reduction scenario and reduced-payment physician payment policy and claims review system.[17]

In Taiwan, the NHI payment policy adopts a unique way in the denial of prescriptions payment, which is called "insurance policy audit and deletion of payments". The auditors act by "post-hoc" denial, or deletion, of payment for the medications. For example, while some health care providers (including psychiatrists) prescribe medications costlier than those prescribed daily by other peer health care providers, auditors could delete the payment for these medications. This doesn't just mean that the NHI denied the payment per se, but also means a 100-fold penalty, that is, 100-fold of the price of the denied medications must be paid back to the NHI by the health care providers.[18–20] The sampling rate of cases for auditing is one-fifteenth (6.67%) of the medical cases submitted monthly by individual health care providers.[21]

MDD is one of the major mental illnesses treated by Taiwanese psychiatrists, many of whom agree that an inadequate poor response to ADT is common. Although 50%–60% of patients respond to first-line treatment, only 35%–40% of patients were reported to experience a remission of symptoms during an initial 8-week trial.[1] In Taiwan, the inadequate response rate has been reported to be 30%. Most psychiatrists in Taiwan agree that around 60% of MDD patients can achieve remission, which is close to that reported with venlafaxine (59.3%), and higher than that reported in previous studies with conventional antidepressants (ie, paroxetine, citalopram, sertraline, fluoxetine, mirtazapine, or other treatments),[22] which may imply that Taiwanese psychiatrists overestimate the MDD remission rate.

Other than medical knowledge and training, physician prescribing behavior is largely influenced by pharmaceutical promotions,[23] health insurance payments, and administrative policy. As previously reported, health insurance policy can jeopardize patient benefits when physicians are required to conform to the finance-driven regulatory rules of health insurance companies.[7,8,24] Switching to venlafaxine, for example, has been shown to have a higher response rate after selective serotonin reuptake inhibitor (SSRI) failure.[22]

Table 3 Multiple logistic regression analyses of the correlate variables associated with aripiprazole and quetiapine

Models/persons	Aripiprazole		Quetiapine	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Crude OR				
<100	1.00 (reference)	–	1.00 (reference)	–
101–200	0.95 (0.54–1.66)	0.860	2.39 (1.43–3.99)	0.001
>200	1.63 (0.63–4.21)	0.311	0.58 (0.29–1.18)	0.133
Adjustment[a] OR				
<100	1.00 (reference)	–	1.00 (reference)	–
101–200	0.94 (0.50–1.77)	0.842	1.93 (1.11–3.36)	0.019
>200	1.44 (0.52–3.99)	0.479	0.36 (0.16–0.78)	0.010

Note: [a]Adjustment for poor response proportion and remission rate.
Abbreviations: OR, odds ratio; CI, confidence interval.

However, in Taiwan, approximately the same number of psychiatrists choose switching as choose augmentation.

Three randomized controlled trials demonstrated that aripiprazole augmentation is useful for antidepressant nonresponders, and that it should be reserved for nonresponders after 6 weeks of adequate ADT.[25,26] There is currently no consensus on the duration of aripiprazole augmentation, however current American Psychiatric Association MDD guidelines recommend the same dose used for the acute phase as in the continuation and maintenance phases.[27] The most common adverse effect of aripiprazole is akathisia, which occurs in about 23.1% of the patients treated with aripiprazole,[25] and can be treated with propranolol. Many Taiwanese psychiatrists choose aripiprazole and quetiapine as augmentation antipsychotics, however up to 30% of Taiwanese psychiatrists still choose off-label olanzapine (34.6%), risperidone (30.2%), and sulpiride (27.4%). In Taiwan, psychiatrists are allowed to prescribe medications for off-label use,[28–31] but off-label use of prescriptions are one of the exclusion criteria for drug relief in the Taiwan Drug Hazard Relief Act, which was enacted in 2000.[32,33]

The main reasons why psychiatrists do not choose aripiprazole are price, insurance audit and deletion, and adverse effects. Aripiprazole costs US$0.33 per mg in Taiwan, and therefore a dose ranging from 2–10 mg/d costs US$0.66–3.30 per day. Whereas, antidepressants cost US$0.14–0.95 per tablet for SSRI, and US$0.90–1.07 per tablet for (serotonin-norepinephrine reuptake inhibitor) SNRI. So an adequate dose of SSRI costs US$0.14–0.95 per day and US$2.70–3.20 per day for SNRI.[34]

The switching strategy is cheaper than augmentation strategy. In 2004, the average daily drug price for depressive outpatients in Taiwan was estimated to be US$1.3±1.316.[35] Insurance payment is an important concern for Taiwan psychiatrists. If the prescription is audited and deleted in outpatients, the penalty is up to 100-fold the medication price.[20] We speculate that insurance audit and deletion is the main reason why Taiwanese psychiatrists do not choose aripiprazole as an augmentation strategy. In contrast to the American Psychiatric Association's willingness to sue insurers over American Medical Association's Current Procedural Terminology code violations,[36] the Taiwanese Society of Psychiatry has taken little action against insurance audit and deletion.

Few previous studies have discussed psychiatrists' decision-making. In one study concerning the prescription of benzodiazepines, the decision-making was found to be influenced by concerns of fear of supply, initiating substance abuse, or even diversions in patients, especially when facing time limits and patient manipulation, however insurance coverage issues were not mentioned.[37] Similar to a study which reported that the prescription of non-steroid anti-inflammatory drugs (NSAIDs) or NSAIDs with gastroprotective therapy to the elderly with osteoarthritis was influenced by the reimbursement policy in Canada,[7] the prescribing behavior by Taiwanese psychiatrists for antipsychotic augmentation seems to be affected by health insurance payment policy.

The response to placebo in antidepressant drug trials for MDD is highly variable and has increased significantly in recent years.[38] Two main mechanisms underlie the effect of placebo administration: conditioned reflexes, which are subconscious, and the patient's expectations, which are conscious. Other factors in placebo administration relate to the doctor's influence on the patient's attitude to his or her disease. This can be referred to as the "context effect".[39] Placebo effects may explain why off-label use of atypical antipsychotics is common among Taiwanese psychiatrists.

The main limitation of this study is lack of demographic data, for most of the psychiatrists did not offer their detailed personal information. However, the total numbers

of psychiatrists was nearly 1,436 in the year of the study, 2012,[40] therefore, nearly one in every five (22.56%) Taiwan psychiatrists responded to this questionnaire, which could be representative of this group.

Conclusion

Antipsychotic augmentation with aripiprazole and quetiapine is recommended for MDD patients with a poor response to ADT, however many Taiwanese psychiatrists still choose a switching strategy. Price and insurance audit and deletion affected the intention to prescribe aripiprazole. We suggest that prescribing behavior by Taiwan psychiatrists for antipsychotic augmentation is affected by health insurance policy.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

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