



LONG-ACTING INJECTABLE ANTIPSYCHOTICS FOR ADHERENCE: THE PHILIPPINE EXPERIENCE

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INTRODUCTION

Psychiatric disorders present a complex pathophysiology that even modern interventions could not directly or fully address. Even to this date, some of these conditions have unknown etymology. That is why the treatment regimen for these conditions tend to be multidisciplinary and have a heavy focus on management of symptoms rather than simply rectifying the cause of disease.

Because of this diverse and complex nature, there are other factors that ultimately influence treatment success. In actual, therapeutic efficacy of medications is just one of many considerations in designing each patient's regimen. Also, due to the elusive nature of the disease, the conditions tend to manifest and be experienced in the long-term hence, adherence and compliance to medication also ranks high in the consideration.

According to Osterberg, medication adherence is a major problem in all areas of medicine, not just psychiatry, where patients have heart disease, diabetes, asthma, epilepsy, or any other condition that requires daily medication. (1) The manifestation of psychiatric disorders can be unpredictable, hence, the need for daily monitoring and medication. One of the biggest challenges to the effectiveness of antipsychotic medications has been ensuring treatment adherence, which is defined as "the extent to which the patient follows medical instructions. (2)

The range of medication non-adherence is reported to be 28-52% for major depressive disorder, 20-50% for bipolar disorder, 20-72% for schizophrenia, and 57% for anxiety disorders. (3) The unpleasant adverse effects of antipsychotic drugs combined with patients' disbelief of having an illness, which is common

among individuals with schizophrenia, result in high rates of non-adherence to antipsychotics in the treatment of schizophrenia.

The armamentarium of psychiatric medications used to treat psychotic, mood and anxiety disorders is increasing and improving. The improvement in the side effect profile and drug efficacy are the fundamental goals for the development of these novel drugs. Since non-adherence was identified as a main contributor in treatment failure, these modern interventions also aim to address this. New developments demonstrate the importance of developing tailored interventions to enable patients to overcome perceptual and practical barriers to adherence.

Long-acting injectable (LAI) antipsychotics are a pharmacologic strategy for treating patients with schizophrenia who relapse due to non-adherence to antipsychotic medication. Rather than the daily pill-taking required with oral antipsychotics, LAI antipsychotics are administered by injection at two- to four-week intervals.

Long-acting injectable (LAI) antipsychotics can play a role in helping patients with schizophrenia remain adherent. (4) Research indicates that patients treated with LAI antipsychotics have decreased hospitalization and use of emergency services compared with those treated with oral antipsychotics. A real-world comparative effectiveness trial that included almost 30,000 patients found that re-hospitalization rates among patients receiving LAIs were 20%-30% lower than for patients receiving equivalent oral formulations. (5) Another double-blind, placebo-controlled, randomized-withdrawal trial involving a long-acting Aripiprazole once

monthly (AOM) injection demonstrated long term efficacy, as signified by a longer time to relapse in patients randomized in the AOM group compared to placebo-treated patients. (6)

Despite the proven efficacy and safety of long-acting antipsychotics, it is unfortunate that this treatment modality is not utilized as often as oral antipsychotics. Acceptance of depot antipsychotics by patients and clinicians is variable and the mode of delivery seems to be a major stumbling block. (7) In a systematic review of patients and nurse attitudes on these LAIs, it was found that while patients on these depot antipsychotics are generally happy with this mode of delivery, citing convenience as main possible reason for preference, there is still no established evidence of clinical superiority of these modalities over the conventional treatment.

THE PHILIPPINE EXPERIENCE

A post marketing surveillance survey was recently conducted on Aripiprazole (Abilify Maintena®), an extended-release injectable suspension of Aripiprazole, administered monthly with a focus on safety and efficacy as per Filipino patients' experience to this long-acting medication (AMPEX). The survey ran from November 2017 to December 2019, enlisting several sites in the Philippines. It aims to provide data on the safety and efficacy of AOM in the treatment of Schizophrenia and Bipolar I disorder, the current approved indications here in the Philippines.

The survey was a multi-center, single group, descriptive survey on male and female patients, aged 18 years and above with Schizophrenia or Bipolar disorder. This was a real-world survey where patients enrolled include those with a diagnosis of schizophrenia, Bipolar disorder, schizoaffective disorders and those deemed by the investigator who would benefit from the medication. (see Fig. 1.) After receiving consent from eligible participants and registration to the survey, the physician proceeded to administer the LAI and schedule the succeeding doses. Safety and efficacy assessment were done during Day 0 (initiation), Day 30 and Day 60 visits.

Safety was assessed based on the reported adverse events (AE) collected during the visits. At the end of the study, among the 328 patients enrolled, 36 patients (11%) experienced adverse

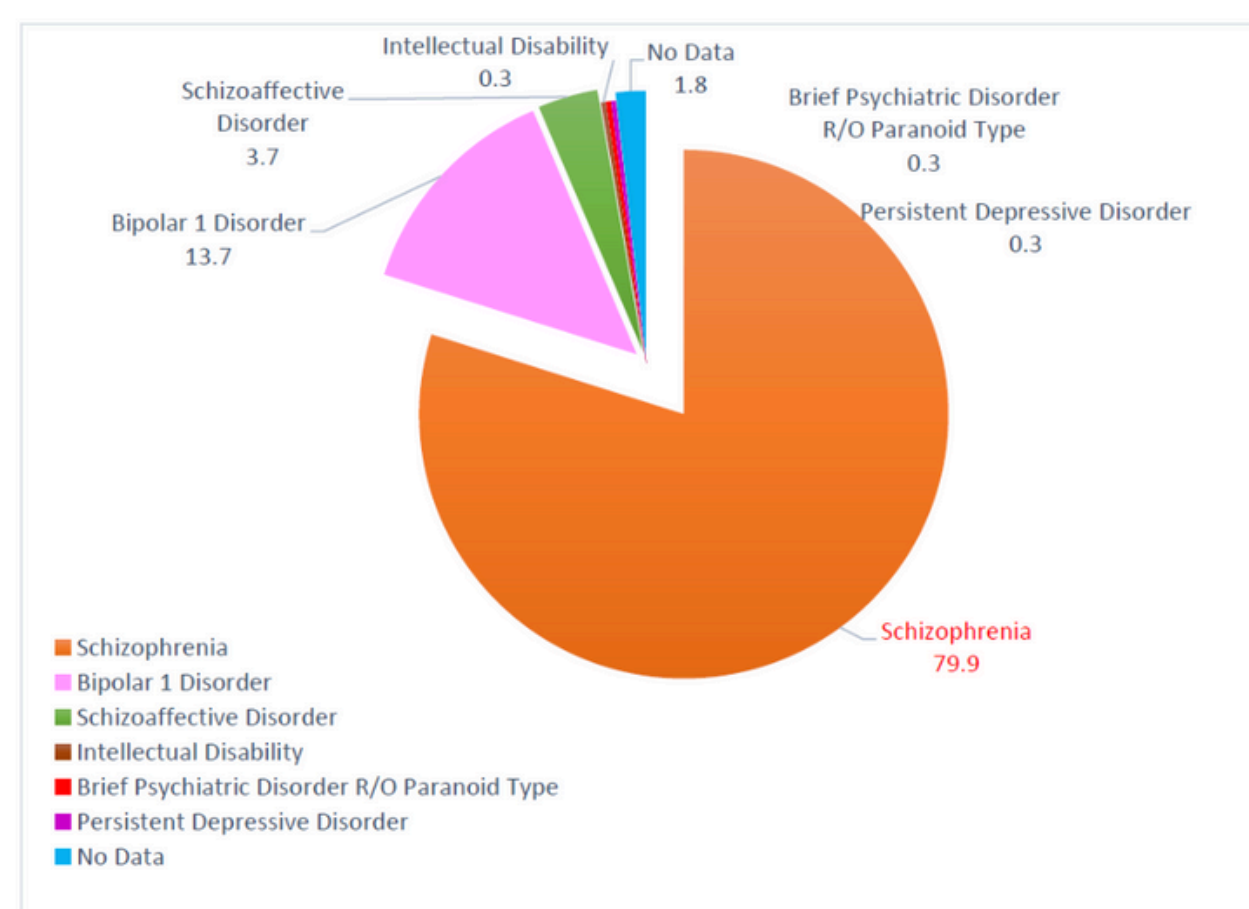


Figure 1. Diagnosis of patients treated with AOM

events. Commonly reported adverse events include Akathisia (3.7%), Fever (1.2%), Rashes (1.2%) and Restlessness (1.2%). These reported adverse events were similar to those observed in various Phase 3 clinical studies of the drug. (8)

Efficacy, on the other hand, was measured using the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression-Improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S) scores. For the efficacy assessment, the Clinical Global Impression (CGI) was used to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. Based on the CGI-I scores gathered during the follow-up visits, 163 (50%) patients showed "Much improvement" in their scores after 60 Days of treatment with the LAI. Based on the CGI-S scores, 90 (27%) of patients reported to be "Markedly Ill" at baseline. Upon Day 30 visit, 111 (34%) patients reported to be "Moderately Ill" on assessment while on Day 60 visits, 115 (35%) of the patients reported to be "Mildly Ill". This exhibited an improvement in the severity experienced by the trial participants.

Table 1. CGI-I scores during Day 30 and Day 60 visits

CGI Improvement Score	AFTER 30 DAYS		AFTER 60 DAYS	
	Frequency	Percentage	Frequency	Percentage
Very Much Improved	14	4%	46	14%
Much Improved	83	25%	163	50%
Minimally Improved	133	41%	32	10%
Minimally Worse	5	2%	1	0.3%
Much Worse	2	1%	1	0.3%
Very much worse	0	0	0	0
No Change	16	5%	3	1%
No Data	75	23%	82	25%
Total	328	100%	328	100%

Table 2. CGI-S scores during baseline, Day 30 and Day 60 visits

CGI Severity Score	BASELINE		AFTER 30 DAYS		AFTER 60 DAYS	
	#	%	#	%	#	%
Extremely Ill	3	0.91	1	0.31	1	0.31
Severely Ill	66	20.12	6	1.83	3	0.91
Markedly Ill	90	27.44	45	13.72	6	1.83
Moderately Ill	76	23.17	111	33.84	60	18.29
Mildly Ill	19	5.79	61	18.60	115	35.06
Borderline Mentally Ill	5	1.5	18	5.49	43	13.11
Normal	3	0.91	10	3.05	18	5.49
No Data	66	20.12	76	23.17	82	25.00
Total	328	100	328	100	328	100

For the Brief Psychiatric Scale (BPRS) scores, there was an improvement noted as evidenced by the reduction of mean BPRS scores from baseline to the follow-up visits.

Table 3. Mean BPRS scores during baseline, Day 30 and Day 60 visits

	<i>Baseline</i>	<i>After 30 Days</i>	<i>After 60 Days</i>
	<i>Mean</i>	<i>Mean</i>	<i>Mean</i>
All Patients (N=245)	66.83	51.84	40.15
Patients with Schizophrenia (N=200)	67.4	52.15	40.14
Patients with Bipolar I Disorder (N=31)	69.06	55.35	44.29
Patients with Other Indications (N=14)	53.79	36.71	31.21

Based on this local survey, it was shown that AOM is safe and efficacious and can be considered as another option in the treatment of Schizophrenia and Bipolar disorders. The survey participants experienced minimal adverse events and had a marked improvement upon initiation of the drug. Despite the low incidence of reported adverse events and the reported marked improvement of symptoms, only 245 (75%) patients were able to complete the survey. The remaining 25% discontinued for various reasons such as lost to follow-up and other unknown reasons. This could be attributed to the fact that the medication was borne out of the patient's pocket and price could be one of the considerations why they opted out and reverted back to their oral medication.

CONCLUSION

Adherence plays a vital role in the success of the treatment and management of psychiatric conditions, as shown by the evidence and data generated by past studies. In the local experience, it was observed that while LAIs offered a simpler and practical approach in

medication administration, the cause of non-adherence is multi-factorial. The reasons for discontinuation during the local post-marketing experience illustrated that even the most convenient and straightforward administration may not be the most practical and preferred approach. Probably, the stigma still lies in the fact that injectable medications are reserved for the more severe and non-compliant patients. Furthermore, since medications are borne out of pocket, financial capability to sustain the medication is a major issue.

Modern approaches including therapeutic and non-pharmacologic modalities should consider factors beyond safety, efficacy and convenience to ultimately promote adherence and this can be a topic of interest that may be explored in the future for the benefit of patients suffering from these long-term conditions.

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