Supplementary material

Survey on the Initiation of Aripiprazole Once-Monthly via a Two-Injection Start in Adult Patients With Schizophrenia: Experience of European Healthcare Professionals

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Table S1. Survey questions.

Question/variable	Response options		Operational definitions/ comments
Questions about you			

What is your primary job role/specialty?	• Physician
	  • General practitioner/ Primary care practitioner
	  • Psychiatrist
	  • Neurologist
	  • Other (specify)
		• Nurse
		  • Psychiatric
		  • Community
		  • Other (specify)
			Categorical variable
			Select one option only

Please select the setting in which you primarily work	• Specialist mental health clinic/centre • Hospital inpatient	• Hospital outpatient • General practitioner • Other (specify)	Select all that apply
How many years have you worked professionally in clinical practice?	Insert number of years		Numerical variable Response limit: 0–80
Considering your total caseload of patients (i.e., all the patients you currently treat/manage), approximately what percentage of patients have schizophrenia?	Insert percentage		Numerical variable Response limit: 0–100
Follow-up question to above: Of your total caseload of patients that have schizophrenia, approximately what percentage of them do you treat with LAIs?	Insert percentage		Numerical variable Response limit: 0–100
As part of your job role, are you mainly responsible for prescribing or administering the AOM 400-TIS initiation regimen to patients with schizophrenia?	• Prescribing • Administration	• Both	Categorical variable Select one option only[a]

Questions about your current use of the AOM 400-TIS initiation regimen in the maintenance setting			
Approximately how long ago did you start prescribing and/or administering the AOM 400-TIS initiation regimen to patients with schizophrenia as maintenance treatment at your treatment centre?	• Less than 6 months ago • 6–12 months ago	• 13–24 months ago • More than 24 months ago	Categorical variable Select one option only
Thinking about your patients who currently receive the AOM 400-TIS initiation regimen for maintenance treatment, what is the average time the patient would spend on oral aripiprazole prior to initiating this regimen?	• Up to 14 days • 14–28 days • More than 28 days		Categorical variable Select one option only
On average, how severe are the symptoms of the typical patients who are initiated with the AOM 400-TIS regimen?	• Mild • Moderate	• Severe	Categorical variable Select all that apply
Based on your recent experience, approximately how old are the typical (adult) patients who are initiated with the AOM 400-TIS regimen at your treatment setting?	• 18–35 years • 36–64 years	• 65+ years	Categorical variable Select all that apply
In what treatment setting is the AOM 400-TIS typically prescribed?	• Inpatient • Outpatient	• Other (specify)	Select all that apply
What are the most common reasons patients with schizophrenia are initiate on the AOM 400-TIS regimen as maintenance treatment after being switched from oral aripiprazole?	• Poor control of positive symptoms • Poor control of all symptoms • Relapse(s) of disease • Poor treatment adherence	• Patient preference (i.e., patient not willing to take oral medication) • High rates of hospitalisations • Other (specify)	Categorical variable Select all that apply
What is your main objective when choosing to prescribe AOM 400-TIS initiation regimen for maintenance treatment?	• I do not prescribe medication as part of my job role • To improve symptoms • To improve adherence • To prevent relapses • To prevent re-hospitalisations	• To reduce hospital length of stay • To avoid the concomitant use of oral aripiprazole • To improve patient quality of life • To reduce burden on patients • Other (specify)	Categorical variable Select all that apply and indicate the primary (most important) objective in your view

What reasons and/or barriers might lead you to not use the AOM 400-TIS initiation regimen for maintenance treatment?	• Lack of reimbursement • Lack of evidence • Patients don't want two injections • Concerns around tolerability	• Concerns around safety of administering high dose on a single day • Lack of clinical education • Other (specify)	Categorical variable Select all that apply
Please indicate the most important patient and clinical factors that influence your decision to prescribe the AOM 400-TIS initiation regimen for maintenance treatment	• I do not prescribe medication as part of my job role • Age at time of treatment • Age at psychotic onset • Number of prior antipsychotics • Adherence to prior treatment • Response to prior treatments • Number of prior episodes	• Number of prior hospitalisations • Length of prior hospital stays • Severity of symptoms • Efficacy • Safety/tolerability • Simplicity and practicality of administration • Patient preference • Patient burden • Other (specify)	Categorical variable Select all that apply Rank 1st, 2nd, and 3rd most important
Aripiprazole is available as an every two-month injection of 960 mg in the USA. If the same formulation was available in Europe, with the option of either a OIS (960 mg IM + 10–20 mg oral aripiprazole for 14 days) and a TIS (960 mg + AOM 400 + oral 20 mg) initiation regimen, which regimen would you choose to use?	• OIS • TIS		Categorical variable Select all that apply

Questions about your wider views and experiences with the AOM 400-TIS initiation regimen		
Based on your recent experience with the AOM 400-TIS initiation regimen as maintenance treatment, please indicate the extent to which you agree or disagree with the following statements:		
The AOM 400-TIS initiation regimen is easy to administer	• Strongly disagree • Disagree • Neither agree nor disagree • Agree • Strongly agree	Categorical variable Select one option
There is a positive impact on symptom severity during maintenance treatment in patients who are initiated with the AOM 400-TIS regimen		
There is a positive impact on relapse frequency during maintenance treatment in patients who are initiated with the AOM 400-TIS regimen		
Patients improve their adherence to aripiprazole treatment after AOM 400-TIS initiation regimen		
The AOM 400-TIS regimen has a similar safety/tolerability profile to the AOM 400-OIS regimen		
Patients who receive the AOM 400-TIS initiation regimen subsequently attend hospital less frequently than those receiving other regimens		
The duration of hospital stays is reduced in patients who receive the AOM 400-TIS initiation regimen		
Patients who receive the AOM 400-TIS initiation regimen appear to be satisfied with this regimen		
Patients who receive TIS appear to be satisfied with a sustained QoL and functional capability		
Overall, I am satisfied with the outcomes of patients treated with the AOM 400-TIS initiation regimen		
Please indicate any other benefits in your opinion associated with the aripiprazole two-injection start regimen	Free text	Insert text in comment box
Please indicate any other barriers or challenges you have experienced in relation to the aripiprazole two-injection start regimen	Free text	Insert text in comment box

[a]Participants must have selected one of the provided answers to be eligible for the survey

AOM 400=aripiprazole once-monthly 400 mg; AOM 400-OIS=aripiprazole once-monthly 400 mg one-injection start; AOM 400-TIS=aripiprazole once-monthly 400 mg two-injection start; IM=intramuscular; LAI=long-acting injectable; OIS=one-injection start; QoL=quality of life; TIS=two-injection start; USA=United States of America

Table S2: Participant free-text responses to the question 'Please indicate any other benefits in your opinion associated with the aripiprazole two-injection start regimen'.

Theme	Participant responses
Improved symptom control/outcomes (n=14)	• **It works well in terms of symptom control** with less metabolic side effects • Better control of positive symptoms • Tolerability, low side effects, **improved relapse periods** • Effectiveness, alternative, hope for better functional level • Excellent outcomes • Fewer relapses • Faster onset of action, **better efficacy** • User-friendliness, **efficacy** • Improved efficacy • **Longer response to therapy**, less effort for the patient and for us as staff • Better adherence, **better efficacy** generally speaking • Patient has fewer doctor's visits, thus better quality of life; **rapid and long-lasting efficacy**, we have less work, compliance is promoted, no need to check whether medication is taken or not • Better control of negative symptoms • Fewer recurrences
Good tolerability/safety profile (n=12)	• It works well in terms of symptom control with **less metabolic side effects** • Generally well tolerated • Better tolerability in terms of extrapyramidal symptoms • **Tolerability, low side effects**, improved relapse periods • Patients are more likely to tolerate medication with fewer negative side effects. Educating and informing patients is an important part of preparation for commencement of the treatment • Low side effect profile • Therapy adherence and **tolerability** • Offers an option that is safer in those with cardiac history • More verifiable tolerability • Tolerability • Safe to use in patients with CVD, good [side effect] profile • Less drowsiness
Improved adherence/ compliance (n=13)	• Removes the risk of non-adherence with oral medication • Easy start, **ensuring compliance** in patients that previously responded to aripiprazole

	• Avoids concerns about oral adherence • It can be difficult to ensure adherence to the oral doses when using the OIS initiation. The two-injection initiation eliminates this problem • Reduction in admissions and **improved compliance with treatment** • Knowing patient is compliant • Improves adherence in the initial phase of long-acting treatment, showing benefits to the patient and eventually making it possible to work on patient compliance in general (service attachment, rehabilitation projects) • High compliance • Safe start of medication with fluctuating compliance • **Better adherence**, better efficacy generally speaking • **Therapy adherence** and tolerability • Patient has fewer doctor's visits, thus better quality of life; rapid and long-lasting efficacy, we have less work, **compliance is promoted, no need to check whether medication is taken or not** • Treatment adherence through 2 visits
Rapid onset of action (n=11)	• Better and quicker loading bolus of aripiprazole • Reduced hospital length of stay, **chance for quicker initiation of treatment** even under emergency conditions • Fast saturation, fast effectiveness • Fast saturation • Reduction of symptomatology in a short period of time • **Faster onset of action**, better efficacy • Patient has fewer doctor's visits, thus better quality of life; **rapid and long-lasting efficacy**, we have less work, compliance is promoted, no need to check whether medication is taken or not • Faster • Less time to coverage, fewer cases of insufficient coverage in the acute phase • Rapid symptomatic remission • Rapid symptom control, especially for patients with extremely short treatment durations who are admitted in a protected manner, and therefore better nursing care less risk to patients and staff
Simple/convenient (n=11)	• Does not need post injection monitoring that LAI olanzapine needs • Simpler for patients, less chance of confusion about starting regimen • **Easy start**, ensuring compliance in patients that previously responded to aripiprazole • Convenient • Very convenient and simple initial treatment • Practicality • Simplicity of treatment management • Patients don't require oral medication • Reduced oral co-administration period

	• Overall easier • Easy to prescribe
Improved patient experience and quality of life (n=10)	• [Stops] you having to distress the patient by having to insist on oral meds too • Easy interaction time with the clients • Patient-friendly approach • **User-friendliness**, efficacy • Psychological well-being • Peace of mind • Patient has fewer doctor's visits, thus **better quality of life**; rapid and long-lasting efficacy, we have less work, compliance is promoted, no need to check whether medication is taken or not • Improved patient's quality of life • Patient's preference • I believe the aripiprazole two-injection has transformed many patients' lives. It has reduced patients' admissions to hospital and has **improved their quality of life**. It has been a revolutionary process for many patients
Improved efficiency and time management for HCPs and patients (n=6)	• Longer response to therapy, **less effort for the patient and for us as staff** • **Patient has fewer doctor's visits**, thus better quality of life; rapid and long-lasting efficacy, **we have less work**, compliance is promoted, no need to check whether medication is taken or not • **Less effort, more time for the patient or for others**, better level of active ingredient • I don't see any benefits here apart from having to spend less time • Patient has to go to the doctor less often, he and we have to sacrifice less time as visits are less frequent • Number of patient contacts would be reduced
Reduced hospitalisation/ re-hospitalisation (n=4)	• **Reduction in admissions** and improved compliance with treatment • Reduced rate of re-hospitalisation • **Reduced hospital length of stay**, chance for quicker initiation of treatment even under emergency conditions • I believe the aripiprazole two-injection has transformed many patients' lives. **It has reduced patients' admissions to hospital** and has improved their quality of life. It has been a revolutionary process for many patients
Stable plasma aripiprazole levels (n=2)	• Achievement of stable level of active ingredient over 24h • More constant plasma levels
Other (n=13)	• One of the cleanest LAIs • Patients refuse oral medication • Regular contact with a mental health professional • Regular visits improve engagement with teams • Frequency • Better understanding of the mental health difficulties to maintain a level of stability • Manageability

	• Modularity in intramuscular drug intake • Initially patients are often easier to convince • The benefit of it being a partial agonist • 2 consultations • Less effort, more time for the patient or for others, **better level of active ingredient** • Tolerability monitoring
No additional benefits identified/supplied (n=13)	• N/A • Not sure • All the benefits AOM400-TIS regimen brings to the patient's quality of life have already been listed above • No problems to comment on • No additional benefits • None • No benefit in percent compared with initial injection alone • No other • I actually don't see any • No additional • None given • [The main advantages … have already been mentioned] • No additional comments

Participant responses were grouped into common themes. Responses may be included in more than one category (text shown in bold refers to the portion of a response that is relevant to the selected category).

AOM 400-TIS=aripiprazole once monthly 400 mg two-injection start; CVD=cardiovascular disease; HCP=healthcare professional; LAI=long-acting injectable; N/A=not applicable; OIS=one-injection start.

Table S3: Participant free-text responses to the question 'Please indicate any other barriers or challenges you have experienced in relation to the aripiprazole two-injection start regimen'.

Theme	Participant responses
Patient unwilling to receive two injections (n=16)	• Having 2 injections at once, patients not keen at times • **Concerns about multiple injections** and tolerability • Patient not always wanting x2 injections • **Patients may dislike the two injections** or show concern about tolerability • Patients dislike the two injections • Patient rejects 2 injections • Patients accepting 2 injections • Some patients don't want the 2 injections, otherwise there are no obstacles • 2 injections could be a problem, but I don't see any concerns there • **Most people reject 2 injections in a row**. And what happens if too much of the active ingredient remains in the body? What are the reactions to this? • Patients don't want 2 injections • It could be a problem cost-wise, **patients may not want 2 injections** • Patients often don't accept 2 injections. Even a continuous injection system requires a lot of convincing • Patients tend to be sceptical about 2 injections, 1 should be enough, they wouldn't be that seriously ill after all • None outside of patient preference for 1 injection only • Patients don't want 2 injections in one day
Patient unwilling (other) (n=11)	• Agreement to begin treatment • A very small number of patients have not accepted the TIS regimen, but this also happens with other treatment regimens and is part of the regular patient management • Persuading patients to participate • Low patient preference • Acceptance from patient • **Patients reject it**, reimbursement is questionable, too much active ingredient in the body • Compliance with 2 injections, **patient's fear** • Uncooperative patient • Patient's refusal • Patient's refusal • Acceptability

Tolerability/side effect concerns (n=10)	• Concerns about multiple injections and **tolerability** • Patients that do not respond to aripiprazole. **Worries about increases side effects** and lack of [easily] accessible information that can be passed on to patients (leaflet, website etc.) • [Extrapyramidal side effects] • Patient tolerability • More likely to expect [extrapyramidal symptoms] • Some fatigue or intolerance events • Patients may dislike the two injections or **show concern about tolerability** • Individual cases with [adverse drug reactions] • Most people reject 2 injections in a row. And what happens if too much of the active ingredient remains in the body? **What are the reactions to this?** • Onset of akathisia
Cost and funding issues (n=9)	• Pricing may make it difficult for some primary care teams to take over prescribing and administration • Cost • Resistance due to cost • Patients reject it, **reimbursement is questionable**, too much active ingredient in the body • **It could be a problem cost-wise**, patients may not want 2 injections • Costs • Funding - in my NHS workplace we have to gain approval from our head pharmacist on a case by case basis • Costs • High costs
Formulary and availability issues (n=5)	• Getting on local formulary • Not on formulary • Sometimes it isn't [on the] formulary, so isn't available in the pharmacy • Immediate drug availability as an order takes time to be distributed to the centre • Difficult to bring in something new
Patient unwilling to receive injections (n=5)	• Patients not liking injections • Patients not willing to have injections • Patient aversion to injections • Injections are unpopular • Injections are not popular with patients
Adherence and compliance concerns (n=5)	• Patient's compliance • Lower compliance • Patient adherence • Poor adherence

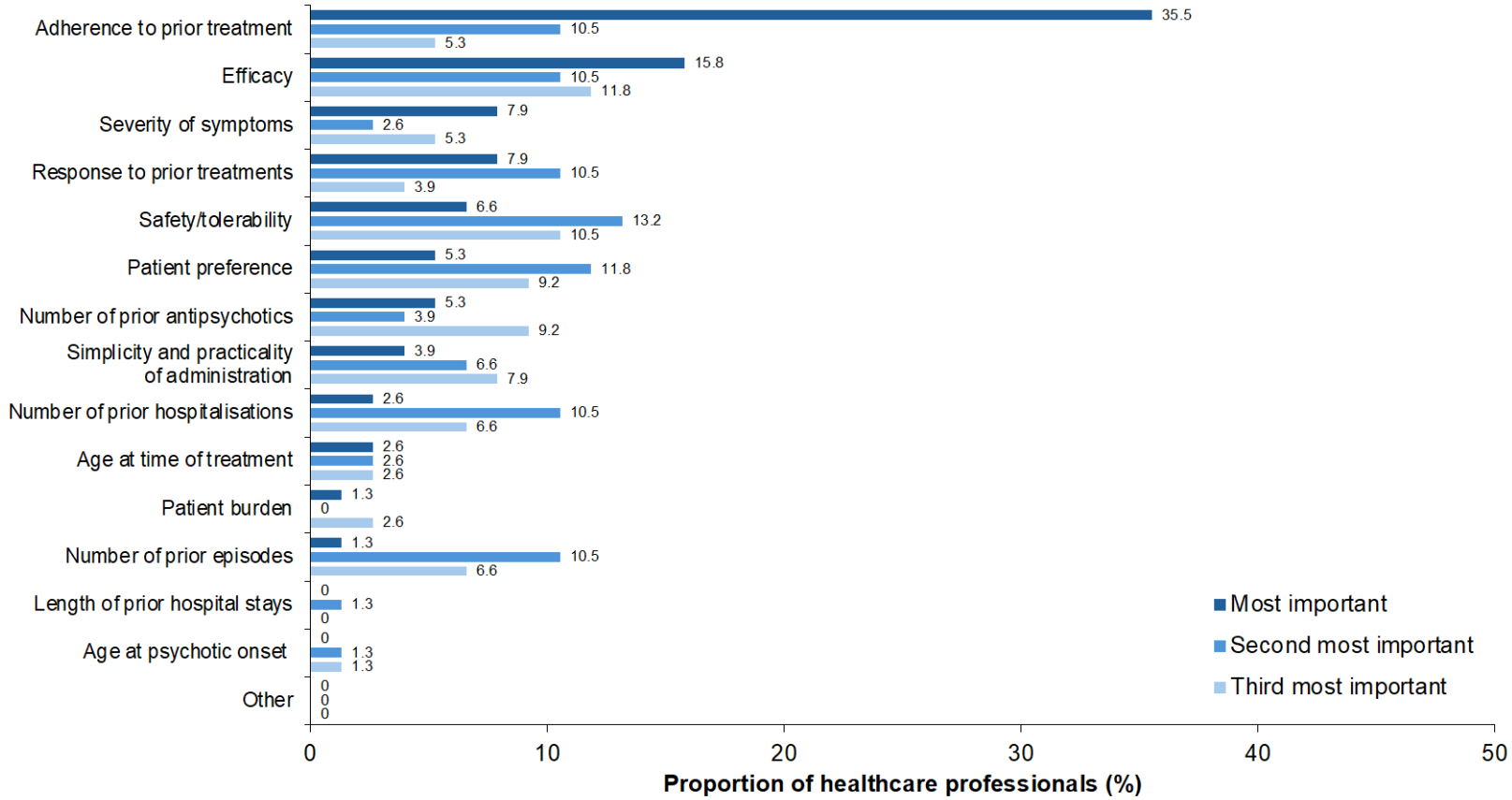
	• **Compliance with 2 injections**, patient's fear
Lack of information, education or experience (n=6)	• Fear from the nurses • Patients that do not respond to aripiprazole. Worries about increases side effects and **lack of [easily] accessible information that can be passed on to patients (leaflet, website etc.)** • Never tested • Not a lot of information to hand • Explanation of rationale for double injection in suspicious or ambivalent patients • Lack of experience
Concerns about dosage/drug accumulation (n=4)	• Can sometimes be perceived as high dosage by the patient • Most people reject 2 injections in a row. And **what happens if too much of the active ingredient remains in the body?** What are the reactions to this? • Problem is, if the drug is injected, then it is a problem to get it out of the body, so to speak, when it would be indicated or necessary • Patients reject it, reimbursement is questionable, **too much active ingredient in the body**
Logistical and scheduling challenges (n=3)	• Patient's unavailability • Organisation • Availability of times and days for administration
Other (n=7)	• **Patients that do not respond to aripiprazole**. Worries about increases side effects and lack of [easily] accessible information that can be passed on to patients (leaflet, website etc.) • If a patient is particularly unwell, it can [be] difficult to administer two separate injections • Reluctance from colleagues • Convenience • Slight difficulty • There have been patients who the 400mg dose has not been effective so they require oral aripiprazole tablets as top ups • Concerns patient, relatives, younger colleagues. Necessary persuasion
No clear barrier or challenge identified/supplied (n=23)	• None • No • None • None • I have not encountered any difficulties • None • None • None • None • None

- None
- None
- None
- None
- I don’t see any at the moment
- None
- N/A
- None
- None
- None
- [No obstacles or challenges that could be mentioned at the moment]
- None
- No specific one

Participant responses were grouped into common themes. Responses may be included in more than one category (text shown in bold refers to the portion of a response that is relevant to the selected category).

N/A=not applicable; NHS=National Health Service; TIS=two-injection start.

Figure S1: Top three most important patient and clinical factors that influence healthcare professionals' decision to prescribe the AOM 400-TIS initiation regimen (N=76)



Data are ranked from the most to least selected response options in the most important category. The denominator was n=76 (all participants [N=94] minus those that did not prescribe as part of their job role [n=18]); 3 respondents did not provide rankings for the 'most important', 3 did not provide rankings for the 'second most important' and 13 did not provide rankings for the 'third most important'.

AOM 400-TIS=aripiprazole once monthly 400 mg two-injection start.