CNS Drugs

Supplementary Material

The Impact of Antipsychotic Formulations on Time to Medication Discontinuation in Patients with Schizophrenia: A Dutch Registry-Based Retrospective Cohort Study

Arnold P.M. van der Lee[1]*; Ibrahim Önsesveren[2]*; André I. Wierdsma[2]; Roos van Westrhenen[3,4]; Aartjan T.F. Beekman[1]; Lieuwe de Haan[5]; Niels C.L. Mulder[2]

* Both authors contributed equally to this work

[1] Department of Psychiatry, Amsterdam University Medical Centre – location VUmc, Amsterdam, The Netherlands;

[2] Department of Psychiatry, Erasmus Medical Centre, Epidemiological and Social Psychiatric Research Institute, Rotterdam, The Netherlands;

[3] Parnassia Psychiatric Institute, Amsterdam, The Netherlands;

[4] Department of Psychiatry & Neuropsychology, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands;

[5] Department of Psychiatry, Amsterdam University Medical Centre – location AMC, Amsterdam, The Netherlands;

Corresponding author:
Arnold P.M. van der Lee, ORCID 0000-0002-1836-5767;
E-mail address: ap.vanderlee@amsterdamumc.nl

1 Methods

1.1 Available prescription data in the database

The following data were available on each medication delivery: delivery date, type of antipsychotic medication, formulation, ATC classification, and the amount of medication, which was expressed in the number of Defined Daily Doses (DDDs). According to the WHO definition, the DDD is the assumed average maintenance dose per day for a medication used for its main indication in adults [1]. For example, 1 DDD Haloperidol oral = 8 mg, and 1 DDD Haloperidol depot =3.3 mg. In the Anatomical Therapeutic Chemical (ATC) classification system, the active substances are divided into different groups according to the organ or system on which they act, and according to their therapeutic, pharmacological and chemical properties. All medication is coded with numbers and letters. For example, the code for antipsychotic medication starts with “N05A”; the ATC code for Haloperidol is “N05AD01”.

1.2 Formulations

All antipsychotic medications were categorized in terms of four formulations: oral-daily, oral-weekly, depot, or mixed, the latter applying when a patient had received any combination of oral-daily, oral-weekly, or depot.

1.3 Estimating average DDD representative for the Netherlands

First, it should be noted that average daily doses as used in the Netherlands, as is the case in all countries, will differ from the theoretical international average WHO doses. This is because patient populations and prescribing preferences differ over countries. To calculate the number of days per patient for whom the antipsychotic medication delivery would be sufficient, we divided the amount of prescribed medication by the average daily doses representative of the Netherlands.

To derive the average daily doses used in the Netherlands, we selected periods of at least 365 days in which patients had received antipsychotic medication without intervals between delivery dates for more than 92 days. In addition, periods were discarded when combinations of formulations were used. The reason for choosing 92 days is that prescriptions are generally supplied for a maximum of 3 months [2, 3]

Over the selected periods, we counted the total number of DDDs and the total number of days covered per prescribed formulation. The Dutch DDD per formulation was the total number of DDDs divided by the total number of days covered per prescription till the next prescription pick-up.

1.4 Antipsychotic status per day

To calculate the number of days and the date until which a prescribed antipsychotic had provided exposure to the medication, we divided the amount of that antipsychotic medication by the corresponding average Dutch DDD (see the calculation example). This enabled us to obtain each patient’s antipsychotic medication status for each day in the study period. There were five overall options for this antipsychotic status: oral-daily, oral-weekly, depot, mixed (any of the possible combinations of the first 3 formulations), or no antipsychotic exposure.

1.5 Calculation example of exposure days

In this example it is calculated how many days a patient is exposed to a sufficient amount of antipsychotics when ten tablets of 10 mg haloperidol are prescribed. Eight mg haloperidol corresponds with 1 DDD haloperidol according to the WHO [1]. A 10-mg tablet corresponds with 1.25 DDD. A prescription of 10 tablets of 10 mg haloperidol was 10 times 1.25 DDD = 12.5 DDD rounded up to 13 exposure days.

Using the average Dutch DDD (which is 1.09 times de WHO DDD, see Table 1), the number of exposure days on a prescription of the same ten 10-mg tablets of haloperidol was 12.5 DDD divided by 1.09 = 11.5, rounded up to 12 exposure days. Using half the average DDDs in the sensitivity analysis (Table S1) the number of exposure days would be: 12.5 DDD/0.54=23.1 rounded up to 24 exposure days and using double the average DDDs (Table S2) it would be: 12.5 DDD/2.17=5.8 rounded up to 6 exposure days.

1.6 References

1. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2013. Oslo, 2012.
2. Dutch medication prescription guideline. [cited; Available from: https://www.rijksoverheid.nl/onderwerpen/geneesmiddelen/vraag-en-antwoord/voor-hoeveel-dagen-mag-mijn-arts-medicijnen-voorschrijven Accessed 10 July 2020.
3. Dutch medication prescription protocol. [cited; Available from: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/medicatie_voorschrijven_nieuwe-_actuele_of_recente_medicatie_-_protocol_nhg_versie_2.2.doc Accessed 10 July 2020.

2 Sensitivity Analyses

2.1 Half and double the average DDDs for the Netherlands and study population

Table 1 (see the main text) presents the average DDDs calculated for the Netherlands, with half the average DDDs in Table S1 and double the average DDDs in Table S2. Using half, average, or double Dutch DDDs lead to different number of days an antipsychotic would be effective for patients. The level used in the three analyses determined if a patient had exposure to antipsychotic medication on December 31, 2015 and if that patient would be selected in that analysis. The lower the doses, the longer the exposure would have been, and the higher the number of patients who would have been exposed to antipsychotics on December 31, 2015. The number of patients in the cohort when using the average Dutch DDDs in the analysis was 8257; the number using half the average Dutch DDDs was 8603, and the number using double the Dutch DDDs was 7818.

2.2 Patient characteristics and history of psychiatric treatment.

Patient characteristics and psychiatric history of the study population using half (Table S1) and double (Table S2) the average Dutch DDDs are comparable with the study population using the average Dutch DDDs (see main text Table 1).

The average number of discontinuation events over 2014-2015 was much lower in the study population selected using half the average DDDs compared with the study population using the average DDDs with higher levels of discontinuation events in the oral-daily and mixed groups. The average number of discontinuation events in the study population selected using double the average DDDs was much higher than the study population using the average DDDs with higher levels of discontinuation events in the oral-daily and mixed groups.

When double the average DDDs were used, the percentage of patients in the short-term group was very high. But in the long-term groups, only six patients were left in the mixed group, too few to indicate reliable survival times. At 45, the number of patients in the oral-weekly long-term group was small.

Table S1 Half the average DDDs; study population, patient characteristics and amount of psychiatric treatment based on half the average DDDs

			Oral-daily		Oral-weekly		Depot		
0.5 * Average DDDs in the Netherlands			1.09		0.75		1.45		
		Baseline antipsychotic formulation status							
		Total	**Oral-daily**		**Oral-weekly**		**Depot**	**Mixed [a]**	
Patients	No. (%)	8603	(100%)	6262	(73%)	473	(5%)	1307	(15%)	561	(7%)
Sex Male	No. (%)	5521	(64%)	3963	(63%)	292	(62%)	884	(68%)	382	(68%)
Age	Mean (SD)	44	(12.0)	44	(12.0)	46	(11.9)	44	(12.1)	43	(11.3)
Male	Mean (SD)	42	(11.6)	42	(11.7)	44	(11.7)	43	(11.7)	41	(11.0)
Female	Mean (SD)	47	(12.0)	47	(12.1)	48	(11.7)	48	(12.1)	46	(11.5)
Subgroup short-term recent antipsychotic use	No. (%)	2424	(28%)	1645	(26%)	98	(21%)	356	(27%)	325	(58%)
Elective psychiatric treatment 2014-2015 (in Euros)	Mean (SD)	7831	(7159)	7257	(6783)	9617	(8409)	9147	(7692)	9667	(7836)
Crisis psychiatric treatment 2014-2015 (in Euros)	Mean (SD)	10115	(26657)	8034	(22742)	14482	(29887)	14012	(33098)	20580	(40189)
Number of discontinuation events 2014-2015											
All patients	Mean (SD)	5	(13.5)	6	(15.3)	3	(7.2)	3	(5.0)	2	(6.2)
	Maximum	105		105		88		53		64	
Subgroup short-term recent antipsychotic use	Mean (SD)	14	(22.0)	19	(25.0)	8	(13.2)	7	(7.3)	3	(7.8)
	Maximum	105		105		88		53		64	
Subgroup long-term recent antipsychotic use	Mean (SD)	1	(3.9)	1	(4.2)	2	(3.6)	2	(2.5)	0	(1.2)
	Maximum	92		92		46		36		12	
Subgroup psychotropic prescription co-medication 2014-2015	No. (%)	6194	(72%)	4651	(74%)	291	(62%)	788	(60%)	464	(83%)
Antipsychotic status at discontinuation in 2016											
Oral-daily	No. (%)	141	(2%)	0	(0%)	1	(0%)	0	(0%)	140	(25%)
Oral-weekly	No. (%)	62	(1%)	0	(0%)	0	(0%)	0	(0%)	62	(11%)
Depot	No. (%)	209	(2%)	0	(0%)	0	(0%)	0	(0%)	209	(37%)
Mixed [a]	No. (%)	262	(3%)	63	(1%)	42	(9%)	149	(11%)	8	(1%)
No antipsychotic medication	No. (%)	4438	(52%)	3550	(57%)	214	(45%)	545	(42%)	129	(23%)
No discontinuation in 2016	No. (%)	3491	(41%)	2649	(42%)	216	(46%)	613	(47%)	13	(2%)

[a] In this table the different mixed combinations of formulations are combined.
DDD Defined Daily Dose
SD Standard Deviation

Table S2 Double the average DDDs; study population, patient characteristics and amount of psychiatric treatment based on double the average DDDs

			Oral-daily		Oral-weekly		Depot			
2 * Average DDDs in the Netherlands			1.09		0.75		1.45			
			Baseline antipsychotic formulation status							
		Total	**Oral-daily**		**Oral-weekly**		**Depot**		**Mixed** [a]	
Patients	No. (%)	7818	(100%)	5896	(75%)	410	(5%)	1079	(14%)	433	(6%)
Sex Male	No. (%)	5040	(64%)	3746	(64%)	252	(61%)	744	(69%)	298	(69%)
Age	Mean (SD)	44	(12.0)	44	(12.0)	46	(11.9)	44	(12.0)	43	(11.5)
Male	Mean (SD)	42	(11.6)	42	(11.6)	44	(11.7)	43	(11.8)	42	(11.1)
Female	Mean (SD)	47	(12.0)	47	(12.1)	49	(11.6)	48	(11.8)	47	(11.3)
Subgroup short-term recent antipsychotic use	No. (%)	6858	(88%)	5076	(86%)	365	(89%)	990	(92%)	427	(99%)
Elective psychiatric treatment 2014-2015 (in Euros)	Mean (SD)	7918	(7184)	7413	(6847)	9897	(8428)	9179	(7798)	9775	(7790)
Crisis psychiatric treatment 2014-2015 (in Euros)	Mean (SD)	9802	(25931)	8172	(22945)	13631	(29180)	13628	(31774)	18850	(38585)
Number of discontinuation events 2014-2015											
All patients	Mean (SD)	30	(31.2)	33	(33.3)	23	(25.9)	15	(11.8)	30	(27.6)
	Maximum	144		144		106		101		107	
Subgroup short-term recent antipsychotic use	Mean (SD)	33	(31.7)	37	(33.7)	24	(26.8)	16	(11.8)	30	(27.6)
	Maximum	144		144		106		101		107	
Subgroup long-term recent antipsychotic use	Mean (SD)	8	(13.9)	8	(14.8)	9	(7.4)	4	(4.2)	3	(5.6)
	Maximum	92		92		28		19		14	
Subgroup psychotropic prescription co-medication 2014-2015	No. (%)	5701	(73%)	4426	(75%)	256	(62%)	657	(61%)	362	(84%)
Antipsychotic status at discontinuation in 2016											
Oral-daily	No. (%)	123	(1%)	0	(0%)	0	(0%)	1	(0%)	122	(22%)
Oral-weekly	No. (%)	45	(1%)	0	(0%)	0	(0%)	0	(0%)	45	(8%)
Depot	No. (%)	156	(2%)	2	(0%)	0	(0%)	0	(0%)	154	(27%)
Mixed [a]	No. (%)	35	(0%)	8	(0%)	6	(1%)	20	(2%)	1	(0%)
No antipsychotic medication	No. (%)	387	(4%)	354	(6%)	13	(3%)	19	(1%)	1	(0%)
No discontinuation in 2016	No. (%)	7072	(82%)	5532	(88%)	391	(83%)	1039	(79%)	110	(20%)

[a] In this table the different mixed combinations of formulations are combined.
DDD Defined Daily Dose
SD Standard Deviation

2.3 Survival Analyses

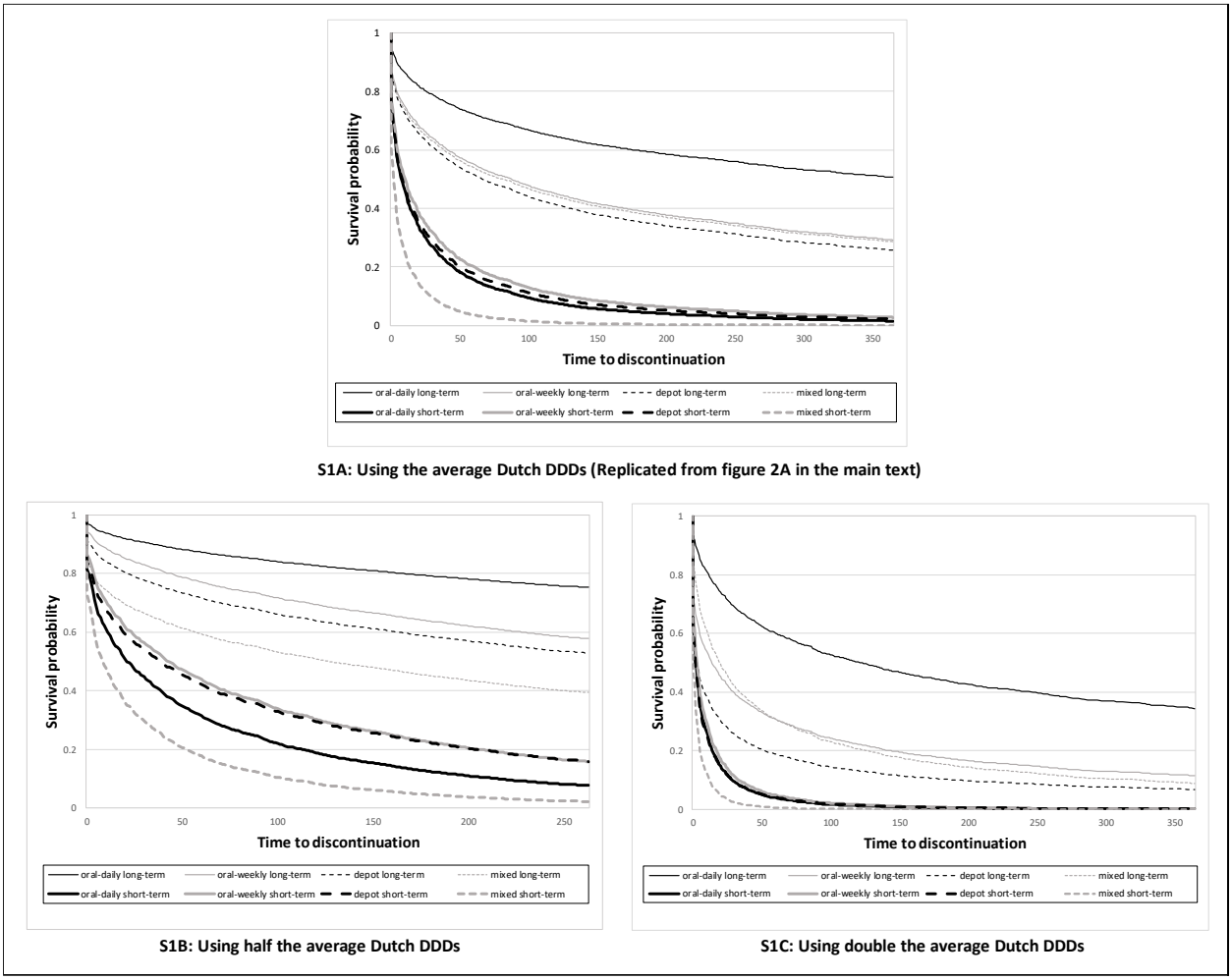
2.3.1 Comparison cox survival: half the average DDD versus the average DDD

Cox survival curve (Fig. S1b) shows the time to discontinuation for the eight baseline antipsychotic formulation status groups using half the average Dutch DDDs. The survival times were higher than when using the average doses (Fig. S1a). Fig. 2a from the main text is replicated in Fig. S1a to make comparisons between the three dose sets possible within this supplement.

The long-term groups, using half the average doses (Fig. S1b), showed the highest survival compared to the short-term groups. The mixed long-term group had the lowest survival of the long-term groups but still much higher than the short-term groups. There was not much difference between the oral-weekly and depot long-term groups. The differences in survival between the short-term groups were larger than when using average doses. The survival time of the oral-daily short-term group was lower than the survival times from oral-weekly and depot, which showed almost the same pattern.

2.3.2 Comparison cox survival: double the average DDD versus the average DDD

Cox survival curve (Fig. S1c) shows the time to discontinuation for the eight baseline antipsychotic formulation status groups using double the average Dutch DDDs. The survival times were lower than when using the average doses (Fig. S1a). The survival time for oral-daily short-term was highest, followed by the oral-weekly and the depot long-term groups. The survival time of all the short-term groups was very short.



DDD Defined Daily Dose

Fig. S1 Cox survival curve time to discontinuation for eight baseline antipsychotic formulation status groups. Groups are defined according to their recent use of the antipsychotic formulation (short-term recent antipsychotic use (60 days or less), versus long-term recent antipsychotic use (61 days or more))