Need adapted use of medication in the Open Dialogue approach for psychosis: A descriptive longitudinal cohort study

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Background:

The open dialogue (OD) approach includes the need-adapted use of psychiatric medication in treating first-episode psychosis (FEP), but there is limited information on how psychiatric medications are actually used in OD-based services. This study aims to analyses long-term medication dispensing patterns among FEP cohort treated according to the OD.

Methods:

The OD cohort consisted of people who received treatment for FEP in the Finnish Western Lapland catchment area at a time of OD implementation (n=61). The comparison group included people whose FEP treatment commenced outside the catchment area during the mid-1990s (n=1378). Data were gathered from national registers from onset to the end of the 10-year follow-up or death. A non-confirmatory descriptive comparison was performed to evaluate the usage patterns and cumulative exposure to psychiatric medication.

Results:

Under OD, a smaller proportion had been dispensed benzodiazepines, antidepressants, and neuroleptics. Persons who had received these medications didn't differ in cumulative exposure. In both groups, most of those who received neuroleptics in the first follow-up years continued using medication throughout follow-up.

Discussion:

OD may assist in detecting FEP patients who can manage without neuroleptics, thus minimizing iatrogenic effects. Due to the observational design, further studies are required to confirm this hypothesis.

Keywords: antidepressants; antipsychotics; anxiolytics; community mental health service; need-adapted treatment; long-term follow-up; risk-benefit ratio; schizophrenia

Introduction

As a component of the Finnish Turku and National schizophrenia projects, the psychotherapeutically-oriented need-adapted approach (NAA) was developed to treat schizophrenia and other non-affective psychoses (Alanen, 2009). The main premise of NAA is the flexible integration of treatment based on the individual characteristics of patients and their families in case by case manner (Lehtinen et al., 2000). In the national schizophrenia project, it was observed that NAA often made it possible to postpone neuroleptics in the treatment of non-affective psychoses, and that in some cases neuroleptics were not needed at all (Alanen, 2009; Lehtinen et al., 2000). In the early 1990s, further research was conducted on the real-world effectiveness of the need-adapted use of psychiatric medication in the treatment of first-episode psychosis (FEP), as part of the quasi-experimental Finnish Acute Psychosis Integrated (API) project (Lehtinen et al., 2000). If the patient's condition had improved via intensive need-adapted treatment, the neuroleptic medication was postponed further, or avoided totally (Lehtinen et al., 2000). If there was a need for alleviation of acute agitation or insomnia at onset, benzodiazepines were used in preference to neuroleptics (Seikkula et al., 2003).

One of the experimental catchment areas in the API project was the Western Lapland region. In the Western Lapland catchment area, a need-adapted and family-oriented care approach was systematically studied and further developed both prior to and after the API study. This eventually led to reorganization of the entire mental health care system to support a more reciprocal response to psychological crises, later known as the Open Dialogue approach (OD) (Seikkula et al., 2006). By emphasizing shared decision- and meaning-making processes, the primary goal in OD is to guarantee both continuity of care and an immediate need-adapted and social network-oriented response, regardless of the diagnosis (Bergström et al., 2022; Seikkula et al., 2011). In naturalistic and register-based cohort studies on all people receiving treatment for FEP within a predetermined inclusion period in the Western Lapland, OD demonstrated promising treatment outcomes,

especially with regard to the longer-term social functioning (Bergström et al., 2018; Seikkula et al., 2011).

Despite the promising results, it remains unclear what factors in OD are beneficial in different situations (Bergström, 2020; Freeman et al., 2019). One of the main distinguishing characteristics of OD as compared to standard care of FEP has been the notably low usage of neuroleptic medication, which is a feature aligned with the main premise of NAA (Bergström et al., 2018). Even though neuroleptics reduce acute psychotic symptoms in the short term (Leucht et al., 2013), many longitudinal studies have shown a reduction in their efficacy over the longer term (Correll et al., 2018). In addition, many iatrogenic effects are known to be associated with long-term cumulative exposure to neuroleptics (Correll et al., 2018; Horowitz et al., 2021; Isohanni et al., 2021). The need-adapted use of psychiatric medication may thus help to optimize the risk-benefit ratio of medication treatment and be one of the factors explaining the favourable outcomes of OD.

As there is still a lack of knowledge regarding the actual risk-benefit ratio in the neuroleptic treatment of FEP in situations where other kinds of support are immediately guaranteed, the Western Lapland cohort provides a unique historical sample of persons whose acute psychosis has been deliberately treated using a maximal psychosocial-orientation, together with a more need-adapted use of psychiatric medication. More detailed knowledge on how psychiatric medication is actually used under OD is important for future research and implementation projects.

The aim of this longitudinal register-based cohort study were to produce descriptive information on the long-term psychiatric medication dispensed to FEP cohort treated according to OD, and to compare the data with standard care.

Methods

Design

The data were formed as part of the ODLONG research project (Bergström, 2020). Register-based information was gathered from a Western Lapland research cohort. The total research cohort included all persons (N=108) who received treatment for non-affective FEP (F20-F29) in the region of Western Lapland during three OD research projects (in the periods 1992–1997 and 2003–2005), who were aged 16–50, and who were treatment naïve at onset.

In order to increase comparability with previous register-based studies (e.g. Torniainen et al., 2015), we used similar methodology to evaluate medication treatment. Since this methodology is based on Finnish national medication dispensation data available only from the year 1995, we excluded persons from the cohort whose treatment was started prior to 1995 *(n*=45). Following the same methodology as in previous studies (Torniainen et al., 2015), we further excluded two cases who had spent over 20% of the follow-up time in hospital; these cases might bias register-based estimation on exposure to neuroleptics, due to the lack of information of medications used during hospital treatment.

The comparison group (CG) was identified from the Finnish National Hospital Discharge Register by including all persons who had one or more register entries with non-affective psychosis (F20–F29) in the years 1995–1996, whose treatment had commenced outside the Western Lapland catchment area, who were aged 16–50, and who were treatment naïve prior to onset (*n*=1763*)*. As with the OD group (see above), cases who spent over 20% of the follow-up time in hospital *(n*=385) were excluded.

The data for both groups were gathered from national social and healthcare registers. The data from the registers were gathered by the Finnish register authorities in the years 2016–2020. The data for OD group was further supplemented with information from original research registers. The total data encompassed the available register entries for all cases prior to 31 December 2015.

Baseline variables

For each case the follow-up time was set to be from onset (first register entry) to 3650 days or death, whichever occurred first. This enabled continuous follow-up for the entire sample.

The baseline variables were formed by combining information from different registers. Somatic morbidity at baseline was evaluated by grouping sample via the Anatomical Therapeutic Chemicals (ATC) classifications, based on first-year medication purchases. From HDR we obtained data on gender, age and Global Assessment Scale (GAS) scores (0 = severe impairment, 100 = superior functioning) at onset, and diagnosis. Most of the psychosis-diagnoses had been set as standard procedure by physicians in their everyday practice. In addition, in line with the methodology of the original research projects (Seikkula et al., 2011), under OD more structured diagnostic procedures to confirm diagnostic criteria of non-affective psychosis were applied at outset on the basis of DSM-III-R (prior 1997) and DSM-IV, with a six-month follow-up.

Validity problems relating to sub-types of non-affective psychosis-diagnoses (Korver-Nieberg, Quee, Boos, & Simons, 2011; van Os & Kapur, 2009) were recognized, as was the fact that in a real-world longitudinal sample, the occurrences of particular psychiatric diagnoses are highly dependent on particular outcomes after FEP, and also on the time spent under mental health services. Due to this and differences in diagnostic procedures between OD and CG, the main focus of this study was on the naturalistic observation of all people in Finland who, for the first-time, received psychiatric treatment for non-affective psychosis within a pre-defined time frame under public mental health services; this was considered to be an indication that a certain symptom threshold in acute mental crisis was exceeded in the clinical context. Nevertheless, because previous research has indicated that schizophrenia-diagnosis can be distinguished by severity level from other non-affective psychoses (Korver-Nieberg et al., 2011), we grouped sample according to whether or not they had at least one register entry with schizophrenia (ICD-9: 295 and ICD-10: F20) within the first year from onset.

Medication usage patterns

We focused on the most commonly used psychiatric medications, using the same ATC codes as in earlier register-based studies (Tiihonen et al., 2016). Thus, we selected all neuroleptics (N05A, except lithium), antidepressants (N06A), and benzodiazepines (N05BA, N05CD, N05CF, N03AE01) that were dispensed from onset to the end of the follow-up. To study temporal changes in the usage patterns of medicines, we observed medication dispensed *prior to* and *after* the first five years from onset.

To evaluate the medication dosage and usage patterns, we created an estimation on cumulative exposure for each medication group, using defined daily doses (DDD) in a similar manner to previous studies (Torniainen et al., 2015; Tiihonen et al., 2016). Thus, we first calculated the sum of the dispensed medications in terms of the DDD. The sum was then divided by the number of follow-up days minus the number of hospital days, bearing in mind that the Finnish national registers do not provide valid information on the medication used during hospital treatment. To study how the overall 10-year cumulative medication exposure was associated with the average time spent in hospital, and with disability allowances, cohort members were categorized into two DDD groups, based on the same cut-off as in previous studies (Bergström et al., 2020): 1) no medication or small/occasional (0–0.5 DDD/day); 2) moderate to high dosages (>0.5 DDD/day).

Statistical methods

As this was a non-confirmatory study on medication dispense patterns, we did not conduct formal hypothesis testing. Instead, the aim was to produce descriptive information on how medication was dispensed after the OD-based treatment of FEP, and how this compared to standard care.

Prior to the analysis, outliers were detected and trimmed via Tukey's fence. Group differences in baseline characteristics and medication usage patterns were studied via descriptive statistics, and by using Chi-square and T-tests. To increase the comparability of the groups, observable baseline variables and loss caused by deaths during follow-up were adjusted via a stabilized inverse

probability of treatment weighting (SIPTW) (Austin & Stuart, 2015). A separate analysis was performed on the medication dispensing patterns for those who had died.

Ethical considerations

The research protocol was reviewed and approved by the North Ostrobothnia Hospital District Ethical Committee (EETTMK: 61/2015).

Results

Sample characteristics

The crude annual incidence of FEP in OD was 15/100 000 persons and in CG 14/100 000 persons. The groups did not differ in gender, diagnosis (schizophrenia vs. other psychoses), GAS-scores, or baseline comorbid somatic conditions. In the OD the persons were younger at onset than in the CG. Following SIPTW there were no further observable differences in covariates (Table 1).

In the OD, two out of the three people (67%) who died during the follow-up had committed suicide. In the CG, 62 out of 138 (42%) had committed suicide. In the OD, all three people (100%) who had died had one or more dispensed neuroleptics prior to their death. Two out of the three (67%) had been dispensed antidepressants, while one (33%) had been dispensed benzodiazepines. In the CG, 95% of those who had died during follow-up had been dispensed neuroleptics, 83 (60%) had been dispensed antidepressants, and 87 (63%) benzodiazepines.

[Table 1]

As compared to OD, at the end of the 10-year follow-up there were relatively more people in CG receiving drug treatment for metabolic (3% vs. 5%) and/or cardiovascular disorders (10% vs. 18%). In OD there were relatively more people receiving treatment for respiratory disorders (12% vs. 11%). In total sample, the 10-year cumulative exposure to neuroleptics were on average higher for those who received treatment for metabolism- (0.7 vs. 0.9 DDD/day) and cardiovascular disorders

(0.7 vs. 0.85 DDD/day). There were no difference in cumulative exposure to neuroleptics of those who received treatment for respiratory disorders at the end of the follow-up as compared to those who didn't (0.7 vs. 0.7 DDD/day).

The average time spent in hospital (1.5% vs. 4.3% of total follow-up time) and on a disability allowance (14% vs. 36% of total follow-up time) during the follow-up was lower in OD than in CG. In both groups those with higher cumulative exposure to any psychiatric medication had also spent more time in hospital and on disability allowances (Table 2).

[Table 2]

Dispensed psychiatric medications

OD had a smaller proportion of people with dispensed benzodiazepines, antidepressants, and neuroleptics over the entire 10-year follow-up. For those receiving dispensed psychiatric medicines, there were no observable differences in cumulative exposures to the medicines in question (Table 3).

[Table 3]

In OD there were more people with no medication dispenses (Table 4). As presented in Table 3, in both groups most of those who had medication dispenses had one or more dispensed medications from all three medication groups. In addition to most used psychiatric medication, there were also fever people in OD with one or more dispensation of mood stabilizers during follow-up (lithium and/or lamotrigine) (2% vs. 9%).

[Table 4]

Temporal changes in dispensed psychiatric medications

Table 5 provides data on the proportion of those who continued or initiated benzodiazepines, antidepressants, and neuroleptics after the first five years. In both groups, the majority of those who

received neuroleptics during the first five years had continued their medication. In both groups, those who continued receiving neuroleptics demonstrated on average a higher cumulative exposure during the last five follow-up years, indicating an increase in average neuroleptic dosage over the follow-up.

[Table 5]

Discussion

As compared to standard care, over the 10-year follow-up, OD was associated with a lesser usage ratio of psychiatric medication after FEP. However, among those who were started on neuroleptics, antidepressants, or benzodiazepines, there were no observable differences in cumulative exposure. It should also be noted that OD reportedly covered the treatment of acute psychosis, and it is possible that some people in the OD cohort had later received treatment in other kinds of psychiatric services. Nevertheless, the initial need-adapted treatment strategy seemed to be associated with stable results, since the majority of those who did not receive neuroleptics during the first years did not dispense neuroleptics in the last follow-up years.

These findings, together with earlier outcome data from partially the same cohort (Bergström et al., 2018), indicate that via OD it may be possible to detect a sub-group of people with acute psychosis who do not need long-term neuroleptic treatment. It is possible that this improves the functional outcome for some patients, given that high cumulative exposure to neuroleptic medication has been associated with many adverse effects (Correll et al., 2018; Bergström et al., 2020; Harrow et al., 2021; Huhtaniska et al., 2017; Joukamaa et al., 2006; Moilanen et al., 2016; Wunderink, 2019). In line with these findings, in both groups, those people who had received more neuroleptics were more likely receiving treatment for metabolism and cardiovascular disorders at the end of the follow-up, and they had also spent longer periods in hospital and on disability allowances. However, this could have been due to confounding by indication, since persons with more severe

symptomatology – and thus poorer outcomes – could be expected to have a higher cumulative exposure to psychiatric medicines over the long follow-up.

It should be noted that OD did not include systematic deprescribing practice and it may be challenging to discontinue already-commenced neuroleptic medication (Horowitz et al., 2021), especially if neuroleptic maintenance treatment has been going on for many years (Tiihonen et al., 2018). Our observations were in line with this notion, since in both groups most persons who had received neuroleptics in the first follow-up years had also continued to dispense them at some point over the entire follow-up. Moreover, for those who had continued medication, the average cumulative exposure to neuroleptics during the last five years was higher than during the first follow-up years.

It is important to note that the findings of this study partially contradict most current treatment guidelines, in which neuroleptics are recommended for both first-line and maintenance treatment of psychosis (Correll et al., 2018). There has also been a general tendency to avoid the use of benzodiazepines in the treatment of psychosis, due to the high risk of dependency (Lader & File, 1987), and of other potential iatrogenic effects reported in some register-based studies (Tiihonen et al., 2016). However, as also demonstrated in this study, comparison of the risk-benefit ratio of neuroleptics and benzodiazepines in a real-world register-based sample is challenging as almost all the FEP patients in the comparison group had received neuroleptics. Moreover, there weren't indications that treating acute FEP via benzodiazepines instead of neuroleptics was associated with increased mortality or dependence in the OD group.

It may well be the case that in the naturalistic samples including only people with a schizophrenia-diagnosis, ongoing neuroleptic medication is associated with a reduced risk of rehospitalization and mortality over a given time frame, as compared to treatment with benzodiazepines and/or no medication at all. However, register-based studies may have overestimated the benefits of neuroleptics as compared to other types of treatment, due to uncontrollable confounding factors and

other methodological limitations (De Hert et al., 2010; Moncrieff & Steingard, 2019; Whitaker, 2020). In addition, most RCTs on the acute antipsychotic effects of neuroleptics have not sufficiently controlled for potential withdrawal effects (Wunderink, 2019; Danborg & Gotzsche, 2019; Horowitz et al., 2021). It is therefore possible that the risk-benefit ratio of neuroleptic medication treatment is different when applied to treatment naïve patients who, at onset, receive immediate intensive psychosocial support and need-adapted drug treatment.

Consequently, there may be a substantial sub-group of people with diagnosed psychosis who would benefit from an alternative form of treatment (Bola et al., 2009), and/or a systematic dose reduction of neuroleptics (Wunderink et al., 2013). This is also supported by recent controlled studies, indicating that neuroleptics may not always be needed in the treatment of FEP, so long as intensive psychosocial support is guaranteed (Francey et al., 2020; Morrison et al., 2020).

Strength and limitations

Finnish registers are valid (Sund, 2012) and reliable sources of information (Sund, 2012; Kiviniemi, 2014). As registers enabled the inclusion of all persons in Finland who received treatment for non-affective FEP within pre-determined timeframe, the results are ecologically valid. However, registers were not originally planned for research purposes, and inaccuracies could arise. For example, the lack of reliable information on outpatient treatment increase the risk that there was an over-representation of patients with more severe symptoms in CG (Bergström, 2020), even if earlier studies indicated that, at the time of inclusion, most patients in Finland with acute psychosis receive hospital and medical treatment (Kiviniemi, 2014; Perälä, 2013), and Hospital Discharge Register alone reliably detected most cases with non-affective psychosis and especially those with a schizophrenia-spectrum diagnosis (Isohanni et al., 1997; Perälä, 2013). Moreover, Northern Finland (including Western Lapland) has traditionally presented a higher prevalence rate for psychosis as compared to rest of Finland (e.g. Perälä, 2013), and these problems are unlikely to remain unreachable in a small region with a low-threshold mental health service; thus, it’s unlikely that

there was an underrepresentation of severe mental health crises in OD as compared to CG. Nevertheless, due to the small population base of Western Lapland, the total n of FEP in OD group remained small, leading to a challenge in reaching firm statistical conclusions.

It should be noted that while in OD the psychosis was diagnosed as a standardized procedure align with the research protocol, in the CG they were diagnosed mainly as part of everyday practice. This might have caused undetected variation in onset symptom severity, hence affecting the comparability of the groups (Bergström, 2020). Since we also lacked information on many social and demographical characteristics, we were not able to fully ensure the comparability of groups, and it's likely that there remained residual confounding. However, one can argue that a non-selective inclusion of all FEP and a general threshold for application of psychosis-diagnosis only in most severe cases potentially increased uniformity of the two groups. Align with this, the incidence and other clinical characteristics in both groups were in line with studies that had previously included FEP patients in real-world settings (Lehtinen et al., 2000; Kirkbride et al., 2009; Svedberg et al., 2001). The comparability of the groups has previously been evaluated and discussed (Bergström, 2020), and we were able to adjust for observable baseline characteristics. Even though for this sub-study we had to exclude some cases, most of the group-characteristics were in line with the total OD cohort (Seikkula et al., 2011; Bergström et al., 2018). However, the proportion of people with dispensed neuroleptics was higher and prevalence of people with schizophrenia-diagnosis lower, mainly due to the inclusion criteria inclusion criteria of this study and an overrepresentation of people from the later inclusion period (see Seikkula et al., 2011).

There are some other limitations. First, the registers lacked information on how the dispensed medication was actually used. The lack of information on medications dispensed during hospital treatment further increased the risk of measurement errors. To increase the comparability with earlier studies (e.g. Torniainen et al., 2015; Tiihonen et al., 2016), we used a similar methodology to estimate the cumulative exposure to medication. It can also be argued that the continuous and

lengthy follow-up time from onset gave reliable information on the actual usage of dispensed medications, since repeated medication dispenses indicate that the prescribed medicines are used.

Conclusion

The OD-based treatment for FEP associate with a stable reduction in treatment via psychiatric medications. This may minimize the risk of iatrogenic medication effects, and thus partially explain the favourable outcomes reported in earlier studies. However, due to observation nature of study and limitations in data, there remains a need to test hypotheses formed from this study via more controlled designs.

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Table 1. Clinical and demographical characteristics prior to and after weighting

	Non-Matched			Inverse probability of treatment weighted samples		
	OD *n*=61	CG *n*=1378	*p*	OD *n*=61	CG *n*=1378	*p*
Adjusted characteristics						
Gender, male	36 (59%)	773 (56%)	0.6	32 (53%)	775 (56%)	0.8

Age (M (SD))	24 (7)	31 (9)	0.001	31 (9)	31 (9)	0.8
Schizophrenia	19 (31%)	412 (30%)	0.8	20 (33%)	413 (30%)	0.5
GAS (M (SD))	33 (10)	35 (12)	0.5	33 (10)	35 (11)	0.2
Comorbidity						
Metabolism	0	9 (1%)	0.5	0	9 (1%)	0.5
Cardiovascular	2 (3%)	144 (10%)	0.1	7 (11%)	140 (10%)	0.6
Respiratory	15 (25%)	428 (31%)	0.3	17 (28%)	424 (31%)	0.7
Death	3 (5%)	138 (10%)	0.2	4 (7%)	135 (10%)	0.4
Dispensed medication						
Benzodiazepines	32 (53%)	941 (68%)	0.01	27 (44%)	938 (68%)	<0.001
High cumulative exposure[a]	10 (16%)	325 (24%)	0.2	9 (15%)	325 (24%)	0.2
Antidepressants	35 (57%)	934 (68%)	0.1	26 (43%)	933 (68%)	<0.001
High cumulative exposure[a]	17 (28%)	462 (33%)	0.1	13 (21%)	462 (33%)	0.1
Neuroleptics	34 (56%)	1343 (98%)	<0.001	33 (54%)	1343 (98%)	<0.001
High cumulative exposure[a]	13 (21%)	760 (55%)	<0.001	14 (23%)	763 (55%)	<0.001

[a]>0.5 DDD/day

Table 2. 10-year cumulative exposure to psychiatric medicines, and average time (%) spent in hospital and on disability allowances

	OD				CG			
	Time (%) spent in hospital in 10-year follow-up		Time (%) spent on disability allowances in 10-year follow-up		Time (%) spent in hospital in 10-year follow-up		Time (%) spent on disability allowances in 10-year follow-up	
Total 10-year cumulative exposure	M(SD)	p	M(SD)	p	M(SD)	p	M(SD)	p
Benzodiazepines		<0.001		<0.001		<0.001		<0.001
High[a]	4% (4)		58% (35)		4% (3)		49% (39)	
Low[b]	1% (2)		5% (17)		5% (4)		32% (37)	
Antidepressants		0.01		0.002		0.2		0.03
High[a]	3% (3)		34% (38)	<0	4% (4)		39% (38)	
Low[b]	1% (2)		8% (23)		4% (3)		34% (39)	
Neuroleptics		<0.001		<0.001		<0.001		<0.001
High[a]	4% (3)		46% (39)		5% (4)		44% (38)	
Low[b]	0.5% (1)		13% (5)		3% (3)		25% (37)	

[a]>0.5 DDD/day
[b]<0.5 DDD/day

Table 3. Purchased psychiatric medication in two follow-up periods

	From onset to day 1825			From day 1825 to day 3650		
	OD *n*=61	CG *n*=1378	*p*	OD *n*=61	CG *n*=1378	*p*
Benzodiazepines	25 (41%)	845 (61%)	0.004	13 (21%)	550 (40%)	0.1
Cumulative exposure, M(SD)[a,b]	0.2 (0.2)	0.4 (0.5)	0.003	0.6 (0.7)	0.5 (0.6)	0.7
Antidepressants	19 (31%)	804 (58%)	<0.001	18 (30%)	640 (46%)	0.02
Cumulative exposure, M(SD)[a,b]	0.5 (0.5)	0.4 (0.5)	0.7	0.6 (0.5)	0.6 (0.5)	0.9
Neuroleptics	23 (38%)	1320 (96%)	<0.001	26 (43%)	1114 (81%)	<0.001
Cumulative exposure, M(SD)[a,b]	0.3 (0.3)	0.34 (0.3)	0.3	0.4 (0.4)	0.5 (0.4)	0.4
Injectable neuroleptics	2 (3%)	240 (17%)	0.01	9 (15%)	171 (12%)	0.6
Clozapine	0	156 (11%)	0.01	2 (3%)	183 (13%)	0.03

[a]Sum of DDDs divided by the length of follow-up

[b]Including only people with one or more dispensed medications

Table 4. Combinations of medication dispenses in two follow-up periods

	From onset to day 1825			From day 1825 to day 3650		
	OD	CG	*p*	OD	CG	*p*
No medication dispenses	27 (46%)	37 (3%)	<0.001	28 (47%)	204 (15%)	<0.001
Benzodiazepines only	5 (9%)	4 (0.5%)	<0.001	0	15 (1%)	0.4
Antidepressants only	2 (3%)	11 (1%)	0.04	4 (7%)	23 (1%)	0.9
Benzodiazepines + antidepressants	2 (3%)	5 (0.5)	0.001	1 (2%)	22 (1%)	0.1
Neuroleptics only	4 (7%)	284 (20%)	0.01	9 (15%)	344 (25%)	0.1
Neuroleptics + benzodiazepines	3 (5%)	250 (18%)	0.01	3 (5%)	175 (13%)	0.1
Neuroleptics + antidepressants	1 (2%)	201 (15%)	0.005	5 (9%)	256 (19%)	0.05
Neuroleptics + benzodiazepines + antidepressants	15 (25%)	587 (42%)	0.01	9 (15%)	339 (25%)	0.1

Table 5. Temporal changes in medication dispensing patterns after the first five years from onset

	OD	CG	*p*
Benzodiazepines continued[a]	10 (42%)	457 (54%)	0.2
Benzodiazepines started[b]	3 (9%)	93 (17%)	0.2
Antidepressants continued[a]	11 (58%)	511 (64%)	0.7
Antidepressants started[b]	7 (18%)	129 (22%)	0.5
Neuroleptics continued[a]	15 (68%)	1091 (83%)	0.1
Neuroleptics started[b]	11 (30%)	22 (39%)	0.4

[a]Including only people with the purchased medications in question within the first five years

[b]Including only people with none of the purchased medications in question within the first five years