AUTHOR Jami Pentinlehto, Marianne Haapea, Lotta Ylitolonen, Anni-Emilia Alakokkare, Solja Niemelä, Jouko Miettunen, Matti Penttilä, Hannu Koponen, Jussi Seppälä, Matti Isohanni, Nina Rautio, Erika Jääskeläinen

TITLE Off-label prescribing of antipsychotics – A questionnaire survey of Finnish physicians

YEAR 2021

DOI

VERSION Publisher's PDF

CITATION Pentinlehto, J., Haapea, M., Ylitolonen, L., Alakokkare, A.-E., Niemelä, S., Miettunen, J., Penttilä, M., Koponen, H., Seppälä, J., Isohanni, M., Rautio, N., & Jääskeläinen, E. (2021). Off-label prescribing of antipsychotics—A questionnaire survey of Finnish physicians. Psychiatria Fennica, 52, 22–48.

JAMI PENTINLEHTO, MARIANNE HAAPEA, LOTTA YLITOLONEN, ANNI-EMILIA ALAKOKKARE, SOLJA NIEMELÄ, JOUKO MIETTUNEN, MATTI PENTTILÄ, HANNU KOPONEN6, JUSSI SEPPÄLÄ, MATTI ISOHANNI, NINA RAUTIO, ERIKA JÄÄSKELÄINEN

OFF-LABEL PRESCRIBING OF ANTIPSYCHOTICS – A QUESTIONNAIRE SURVEY OF FINNISH PHYSICIANS

ABSTRACT

Antipsychotics (APs), especially second-generation antipsychotics, are being increasingly used around the world. At the same time their off-label use has also increased worldwide, as well as in Finland. The aim of our study was to find out the off-label prescribing of APs in Finland among physicians in different healthcare units. The study was conducted as a questionnaire survey. Particular attention was paid to practices between psychiatrists and other physicians (mostly general practitioners and occupational health doctors). Similar studies have not been conducted on this topic in Finland before. Altogether 216 physicians answered the questionnaire. The most common indications for off-label prescription were insomnia and anxiety, and this was evident for both psychiatrists as well as other physicians. Quetiapine was the one most commonly prescribed off-label AP. Over one-third of psychiatrists (39%) and about one-third of other physicians (30%) did not give instructions on the length of the treatment. The metabolic values were reported to be followed by 44% of the psychiatrists and by 18% of other physicians. Nearly two-thirds of all respondents thought that off-label use had more benefits than harms. Compared to other physicians, psychiatrists prescribed APs for off-label use more frequently and for more varied psychiatric conditions. Off-label use of APs seems to be a clinical reality in Finland. There is need for further studies on efficacy and adverse effects of APs in off-label use, and also a need for clinical guidelines on monitoring the patients using APs off-label.

KEY WORDS: OFF-LABEL, ANTIPSYCHOTIC, QUETIAPINE, PRESCRIPTION, INSOMNIA, ANXIETY, DEPRESSION, PSYCHOPHARMACOLOGY, INDICATION

INTRODUCTION

Off-label use means the use of pharmacological drugs for an unapproved indication (1). It can also indicate use by an age group or dose outside of the official recommendations. Estimates of the proportion of off-label prescriptions out of all prescriptions in medicine vary between 11-21% (2,3).

A study on international trends in antipsychotic (AP) use found that between the years 2005 and 2014, two-thirds of the studied populations (16 countries, including Finland) had an increase in AP utilization, mainly due to increased second-generation antipsychotic (SGAP) use (4). Finland had the second highest relative increase in the prevalence of SGAP use (179%). In many countries quetiapine had become the most commonly prescribed AP drug during the study period in all age groups (4). The increase in use of SGAPs has been mostly due to increased off-label use (5).

For on-label use, indications for SGAPs in Finland are psychosis, bipolar disorder, aggression in dementia and behavioural disorders (risperidone only), and adjunctive therapy for major depression (long-acting quetiapine only) (6-8). In 2019, APs were prescribed to more than 200 000 Finns, which is around 4% of the population (9).

According to a systematic review in adult populations, AP off-label prescriptions varied from 40% to 75% of all AP users, and the indications were typically for mood disorders, insomnia, anxiety disorders and agitation (5). Quetiapine was the most often prescribed AP, especially for anxiety and insomnia for adults. For children and adolescents 36-93% of AP prescriptions were off-label, since most APs do not have an indication for persons under 18 years, not even for psychotic disorders. Children with off-label use of antipsychotics have most commonly had disorders such as attention deficit hyperactivity disorder (ADHD), oppositional disorders, conduct disorders, pervasive developmental disorders, tics, schizophrenia, depression, anxiety disorders and bipolar disorders. Risperidone was the most commonly prescribed drug for children. Among elderly people, off-label prescriptions covered 22-86% of all AP prescriptions, mostly for behavioural issues, depression, dementia, insomnia and anxiety disorders (5).

There is some evidence for the efficacy of APs in off-label use. In 2011, Maglione et al. (10) conducted an extensive systematic review which concluded that olanzapine, risperidone and aripiprazole are associated with benefits for the treatment of behavioural symptoms in dementia. Quetiapine has shown efficacy for the treatment of generalized anxiety disorder and as an augmentation treatment for depression, and risperidone in the treatment of obsessive-compulsive disorder (OCD). On the other hand, the review found that there are also significant side effects and that the response to treatment is individual (10).

Regarding primary insomnia, the use of quetiapine for treatment has been evaluated in only one randomized, double-blind, placebo-controlled trial of 13 patients (11), and in one open-label pilot study of 18 patients (12). Both of these had short follow-ups (2 and 6 weeks). The open-label study found improvement in sleep parameters (sleep quality, total sleep time and sleep efficiency), while the randomized controlled trial (RCT) did not find statistically significant improvement. There is some evidence for quetiapine in the treatment of secondary insomnia (13).

No research has been conducted on the prescribing and experiences of APs in off-label use in Finland before. Based on clinical experience, off-label prescriptions for APs have increased, especially in primary care and especially for the use of quetiapine for insomnia. This view is supported by reports from the Social Insurance Institution of Finland. According to the reports between 2008 and 2018, the number of users of APs had increased 46%, and for quetiapine the increase of users had been even greater (126%). Also, the proportion of off-label users among all AP users increased: in 2008 approximately 48%, and in 2018 63%, of all who used APs used them without reimbursement for psychoses or similar severe conditions, indicating off-label use (14). In addition, little is known about how often physicians monitor cardiometabolic risk factors in their patients when using APs off-label (15). Thus, off-label use and prescribing habits are common, clinically important and complicated issues needing further studies.

AIM OF THE STUDY

The aim of this study was to find out the off-label prescribing of APs in Finland among physicians in different healthcare units. We were especially interested in differences between psychiatrists and other physicians.

MATERIAL AND METHODS

A questionnaire survey on off-label prescribing of APs was sent to 1195 physicians during May–October 2019. The survey was made by using REDCap-application (Research Electronic Data Capture, https://www.project-redcap.org), which has been developed for data collection in clinical trials (16,17). The sample included physicians from various healthcare facilities and organizations who prescribe medication for mental illness (18).

Lead physicians or liaisons were sent an invitation to participate in the study and a request to send a questionnaire to the physicians working in their organization. The invitation was re-sent once if the lead physicians or liaisons did not respond to the first invitation. Furthermore, they were asked to report on how many physicians the questionnaire was forwarded to. A total of 216 physicians (18%) responded to the survey.

The organizations were selected systematically and by convenience sampling. The questionnaire was sent to healthcare centres and mental healthcare services of all cities with a university hospital and to all university hospital psychiatric clinics. In addition, as a method of convenience sampling, participation was asked from the largest occupational health services in Oulu and health centres in the Oulu area, and the health centres of South Karelia Social and Health District. To include the Northern part of Finland, health centres and mental health services from Rovaniemi and the Lapland Central Hospital were also asked to participate.

The answers were received from health centres or stations in the following locations: Oulu, Muhos, Rovaniemi, Kuopio, Turku, Tampere and the health centres of South Karelia Social and Health District. Psychiatric outpatient clinics and departments also participated in the following regions: Oulu University Hospital (OYS), Kuopio University Hospital (KYS), Turku University Hospital (TYKS), Tampere University Hospital (TAYS) (adult psychiatry) and the Lapland Central Hospital. Mental health services from Oulu, Tampere and Rovaniemi also participated. In addition, the following occupational health units from the Oulu region were involved: Virta, Mehiläinen and Terveystalo.

The questionnaire included a total of 23 questions surveying physicians' background information, antipsychotic prescribing for off-label use, frequency of off-label prescriptions, medications and dosages, follow-up of patients and the advantages and disadvantages of off-label use. (*Electronic attachment 1*)

Identification data was not collected in the survey and the phrasing of questions were made so that the respondent could not be identified. The University of Oulu Ethics Committee for the Humanities stated in March 2019 that there was no need for an ethics statement for this survey.

The results of the study are presented using frequency distributions and cross-tabulations. Particular attention in this article was paid to practices between psychiatrists and other physicians so we made two groups of respondents, psychiatrists (including adult psychiatry, child psychiatry, adolescent psychiatry, forensic psychiatry and geriatrics) and other physicians, and compared their answers using cross-tabulation. Geriatrics were combined with psychiatrists since geriatrics have specialty training on the use of drugs, including APs, in old people who are relatively commonly prescribed APs off-label. In addition, the group "other physicians" includes mainly physicians working in primary care and occupational healthcare. Statistical analyses were made using IBM SPSS Statistics, version 25.

RESULTS

CHARACTERISTICS OF THE SAMPLE

Altogether 216 physicians answered the questionnaire. More than two-thirds of the respondents were women (69%) (Table 1). The age of the respondents was evenly distributed, 78% of the sample being 31-60 years of age. Nearly all respondents worked in the field of either psychiatry (44.5%) or general practice/occupational healthcare (50.2%).

Respondents were fairly experienced physicians, since almost 65% had more than 10 years and only 20% had less than 5 years of work experience. The majority of respondents were from the area of the Northern Ostrobothnia Hospital District (42.8%), and the rest fairly evenly from other hospital districts participating in the survey from Lapland to Southern and Eastern Finland.

Table 1. Background information of the sample (n=216)

	N	(%)
Gender[1]		
Men	67	31.2
Women	148	68.8
Age group		
Under 31 years	31	14.4
31-40 years	65	30.1
41-50 years	50	23.1
51-60 years	54	25.0
Over 60 years	16	7.4
Situation of specialization[1]		
Physician	30	14.0
In specialist training or specialist	185	86.0
Field of specialization[2]		
Psychiatry	94	44.5
Geriatrics	5	2.4
General practice/occupational healthcare	106	50.2
Other[3]	6	2.8
Working years		
Under 5 years	44	20.4
5-10 years	33	15.3
11-20 years	55	25.5
21-30 years	49	22.7
Over 30 years	35	16.2

Healthcare sector[4]		
Health centre/station/Ward of a health centre/Maternity clinic	72	33.3
Occupational health service	42	19.4
Outpatient unit for mental health services/Substance abuse services/Outpatient clinic of a psychiatric hospital/Ward of a psychiatric hospital	100	46.3
Private health clinic	16	7.4
Hospital District[1]		
Northern Ostrobothnia	92	42.8
Southwest Finland	29	13.5
Pirkanmaa	30	14.0
North Savo	22	10.2
South Karelia	19	8.8
Lapland	23	10.7

[1]missing data n=1
[2]missing data n=5
[3]gynaecology, paediatrics, otorhinolaryngology, internal medicine
[4]it was possible to choose several answer options in this question

PRESCRIPTION PATTERNS

In total, 94% of the respondents had prescribed APs for off-label indications and almost every fourth (23%) had prescribed them at least once a week (Table 2). Those who renewed off-label prescriptions a few times a week or at least once a month accounted for 64% of the total respondents. 39% (43/110) of those who were not psychiatrists or geriatricians did not usually consult a psychiatrist or geriatrician before prescribing APs for off-label use.

The most common indications for off-label prescription were insomnia (83%) and anxiety (45%). Quetiapine (87%) and olanzapine (22%) were the most often prescribed AP. The physicians were asked to report the most common dose or range of dose for the drugs they prescribed, and most of them reported the range of dose. For quetiapine, the most commonly reported minimum doses were 25mg (n=146) and 12.5mg (n=26), and the most commonly reported highest doses were 100mg (n=59), 50mg (n=53) and 25mg (n=37). For olanzapine, the most common minimum doses were 5mg (n=30) and 2.5mg (n=27), and the most common maximum doses were 5mg (n=22) and 10mg (n=22). The respondents instructed a patient to use the AP most commonly for 1-3 months (37%). More than a third (35%) did not give instructions on the length of the treatment.

The majority of the respondents (88%) monitored the clinical status of the patient. They most commonly followed change in symptoms, change in functional capacity and side effects of medication. Two-thirds of the physicians thought that there are more benefits than harms in off-label use of antipsychotics. Typical benefits were decrease of insomnia (86%), relief of anxiety (67%) and mood stabilization (44%), while typical disadvantages were fatigue (88%), weight gain (49%) and dry mouth (27%).

Table 2. Prescription patterns of APs in off-label use.

	N	(%)
On average, how often do you prescribe antipsychotics for an illness or symptoms for which there is no official indication? [1]		
daily	2	1.0
a few times a week or about once a week	44	22.4
every 1-2 weeks or about once a month	60	30.6
rarely	85	43.4
never	5	2.6
On average, how often do you renew an antipsychotic prescription for an illness or symptoms for which there is no official indication? [2]		
daily	3	1.5
a few times a week or about once a week	53	26.6
every 1-2 weeks or about once a month	74	37.2
rarely	65	32.7
never	4	2.0

Do you consult a psychiatrist, geriatrician, adolescent psychiatrist or child psychiatrist before prescribing an antipsychotic without an official indication? [3]		
I do not consult	43	21.7
yes, I always or almost always consult	14	7.1
yes, I sometimes consult	53	26.8
I am a psychiatrist, geriatrician, adolescent psychiatrist, or child psychiatrist or specializing in them	88	44.4
For what symptom or illness do you most commonly prescribe an antipsychotic when the drug has no official indication for it? [4]		
anxiety	97	44.9
insomnia	179	82.9
unipolar non-psychotic depression	26	12.0
neuropsychiatric disorders	2	0.9
borderline personality disorder	35	16.2
substance abuse disorders	17	7.9
aggression in dementia	29	13.4
some other	11	5.1
What antipsychotics do you usually prescribe without an official indication? [4]		
quetiapine	188	87.0
risperidone	32	14.8
olanzapine	47	21.8
aripiprazole	33	15.3
perphenazine	5	2.3
some other	9	4.2
How long do you usually instruct a patient to use an antipsychotic without an official indication? [4]		
up to a few weeks	44	20.4
1-3 months	79	36.6

3-6 months	32	14.8
6-12 months	13	6.0
over 12 months	9	4.2
I do not give instructions on the length of treatment	75	34.7
Do you monitor the clinical status of these patients? [5]		
no	23	11.9
yes	171	88.1
If you do monitor, what parameters do you follow? [4]		
change in symptoms	168	77.8
change in functional capacity	142	65.7
metabolic values	66	30.6
other somatic condition	79	36.6
side effects of medication	141	65.3
some other	15	6.9
What benefits have you noticed from using antipsychotics without an official indication? [4]		
mood rising	37	17.1
mood stabilizing	94	43.5
relief of anxiety	145	67.1
decrease of insomnia	185	85.6
relief of agitation or aggression	90	41.7
somatic condition improvement	89	41.2
some other	5	2.3
What disadvantages have you noticed in the use of antipsychotics without an official indication? [4]		
fatigue or excessive sleepiness	174	80.6
extrapyramidal symptoms	54	25.0

mood decreasing	11	5.1
anhedonia (inability to feel pleasure)	41	19.0
weight gain	106	49.1
rise in cholesterol levels	38	17.6
effects on blood pressure or heart rate	45	20.8
dry mouth	58	26.9
some other	18	8.3
In your experience, is there more benefit or harm from using antipsychotics without an official indication?		
more benefits	133	68.2
more harm	1	0.5
equally harms and benefits	61	31.3

[1] missing data n=20
[2] missing data n=17
[3] missing data n=18
[4] it was possible to choose several answer options in this question
[5] missing data n=22

COMPARISON BETWEEN THE PSYCHIATRISTS AND OTHER PHYSICIANS

Psychiatrists prescribed APs for off-label use usually about once a week (34%), once a month (33%) or rarely (30%), whereas most of the other physicians prescribed them rarely (57%) or about once a month (29%) (Table 3). Both psychiatrists and other physicians prescribed APs off-label most commonly for insomnia and anxiety. The psychiatrists, on the other hand, prescribed APs ten times more often for unipolar non-psychotic depression and fifteen times more for borderline personality disorder than other physicians.

The most commonly prescribed APs among psychiatrists were quetiapine (92%), olanzapine (36%) and aripiprazole (28%). Similarly, among physicians other than psychiatrists, quetiapine (82%) was the most commonly prescribed AP, whereas other APs were less frequently prescribed. In both groups the minimum dose of quetiapine was most often 25mg (psychiatrists n=72, others n=69), but the most common maximum doses were higher among psychiatrists (100mg, n=42) than among other physicians (50mg, n=38). Psychiatrists also prescribed on average higher doses.

Over one-third of psychiatrists (39%) and about one-third of other physicians (30%) did not give instructions on the length of the treatment. Among psychiatrists 85%, and among other physicians 90%, monitored the clinical status of patients. Both psychiatrists and other physicians followed most frequently the change in mental symptoms, side effects of medication and change in functional capacity. The metabolic values were followed by 44% of the psychiatrists and by 18% of other physicians. Psychiatrists had noticed more often and more varied disadvantages, i.e. side effects of off-label APs. Among both psychiatrists and other physicians, the most frequently noticed side effects were fatigue and weight gain.

Table 3. Comparison between psychiatrists and other physicians

	Psychiatrists[1] (n=99) N (%)	**Other physicians** (n= 112) N (%)
On average, how often do you prescribe antipsychotics for an illness or symptoms for which there is no official indication?[3]		
daily	2 (2.0)	0 (0.0)
a few times a week or about once a week	33 (33.7)	10 (10.6)
every 1-2 weeks or about once a month	32 (32.7)	27 (28.7)
rarely	29 (29.6)	54 (57.4)
never	2 (1.0)	3 (3.2)
On average, how often do you renew antipsychotic prescription for an illness or symptoms for which there is no official indication?[4]		
daily	3 (3.1)	0 (0.0)
a few times a week or about once a week	25 (25.5)	27 (28.1)
every 1-2 weeks or about once a month	32 (32.7)	39 (40.6)

→

rarely	35 (35.7)	29 (30.2)
never	3 (3.1)	1 (1.0)
For what symptom or illness do you most commonly prescribe an antipsychotic when the drug has no official indication for it? [2]		
anxiety	63 (63.6)	30 (26.8)
insomnia	88 (88.9)	86 (76.8)
unipolar non-psychotic depression	22 (22.2)	2 (1.8)
neuropsychiatric disorders	1 (1.0)	1 (0.9)
borderline personality disorder	33 (33.3)	2 (1.8)
substance abuse disorders	12 (12.1)	5 (4.5)
aggression in dementia	10 (10.1)	18 (18.1)
some other	8 (8.1)	3 (2.7)
What antipsychotics do you usually prescribe without an official indication? [2]		
quetiapine	91 (91.9)	92 (82.1)
risperidone	22 (22.2)	8 (7.1)
olanzapine	36 (36.4)	7 (6.3)
aripiprazole	28 (28.3)	4 (3.6)
perphenazine	2 (2.0)	1 (0.9)
some other	5 (5.1)	3 (2.7)
How long do you usually instruct a patient to use an antipsychotic without an official indication? [2]		
up to a few weeks	16 (16.2)	27 (24.1)
1-3 months	40 (40.4)	37 (33.0)
3-6 months	13 (13.1)	18 (16.1)
6-12 months	8 (8.1)	4 (3.6)
over 12 months	4 (4.0)	5 (4.5)
I do not give instructions on the length of treatment	39 (39.4)	34 (30.4)

Do you monitor the clinical status of these patients? [5]		
no	14 (14.7)	9 (9.6)
yes	81 (85.3)	85 (90.4)
If you follow, what things do you follow?[2]		
change in mental symptoms	82 (82.8)	81 (72.3)
change in functional capacity	71 (71.7)	66 (58.9)
metabolic values	44 (44.4)	18 (16.1)
other somatic condition	40 (40.4)	35 (31.3)
side effects of medication	77 (77.8)	60 (53.6)
some other	5 (5.1)	10 (8.9)
What benefits have you noticed from using antipsychotics without an official indication? [2]		
mood rising	24 (24.2)	11 (9.8)
mood stabilizing	61 (61.6)	29 (25.9)
relief of anxiety	82 (82.8)	58 (51.8)
decrease of insomnia	90 (90.9)	90 (80.4)
relief of agitation or aggression	54 (54.5)	33 (29.5)
somatic condition improvement	50 (50.5)	35 (31.3)
some other	3 (3.0)	2 (1.8)
What disadvantages have you noticed in the use of antipsychotics without an official indication? [2]		
fatigue or excessive sleepiness	92 (92.9)	77 (68.8)
extrapyramidal symptoms	33 (33.3)	17 (15.2)
mood decreasing	10 (10.1)	0 (0.00)
anhedonia (inability to feel pleasure)	32 (32.3)	7 (6.3)
weight gain	69 (69.7)	34 (30.4)
rise in cholesterol levels	31 (31.3)	4 (3.6)
effects on blood pressure or heart rate	32 (32.3)	10 (8.9)

dry mouth	41 (41.4)	13 (11.6)
some other	8 (8.1)	9 (8.0)
In your experience, is there more benefit or harm from using antipsychotics without an official indication?[6]		
more benefits	67 (69.8)	62 (66.0)
more harm	1 (1.0)	0 (0.00)
equally harms and benefits	28 (29.2)	32 (34.0)

[1]among respondents in the psychiatry group there were 81 adult psychiatrists and 5 geriatricians
[2]it was possible to choose several answer options in this question, missing data n=5
[3]missing data n=24
[4]missing data n=22
[5]missing data n=27
[6]missing data n=26

RESPONDERS' THOUGHTS ON ANTIPSYCHOTIC OFF-LABEL USE AND PRESCRIPTIONS

Of the open questions of the questionnaire, for example, the following selected notions were made. The side-effects were considered small due to the small doses used. However, some of the responders noted that metabolic values and potential other adverse effects should be monitored more closely. There was a requirement for more options for psychosocial treatment of insomnia. The risks of tolerance and addiction when using quetiapine were considered smaller than when using benzodiazepines long-term. The importance of carefully choosing the patients for whom off-label use was recommended. In addition, clearer guidance on off-label prescribing of APs was considered necessary.

DISCUSSION

MAIN RESULTS

According to our survey, off-label prescription of APs is relatively common among psychiatrists and also physicians working in primary and occupational healthcare. Quetiapine was the most commonly prescribed off-label AP, the second most common being olanzapine. Doses were usually relatively small.

Most common indications for off-label prescription were insomnia and anxiety, and this was evident for both psychiatrists as well as other physicians. Over one-third of psychiatrists (39%) and about one-third of other physicians (30%) did not give instructions on the length of the treatment. The metabolic values were followed by 44% of the psychiatrists and by 18% of other physicians. Nearly two-thirds of all physicians thought that off-label use had more benefits than harm.

In our sample, almost all respondents had prescribed APs for off-label use. Since response rates were rather low, our sample may have highlighted those who prescribe APs in their work on a relatively regular basis. Therefore, the actual number of physicians who prescribe APs off-label may be biased. However, the results on off-label prescription practices among those who do prescribe APs off-label are more valid.

COMPARISON TO EARLIER STUDIES

There are relatively few previous questionnaire studies on physicians about AP off-label use. One questionnaire survey of psychiatrists in Canterbury, New Zealand has been conducted to estimate the frequency and characteristics of off-label use. Psychiatrists were identified through the website of the New Zealand Medical Council and were sent the questionnaire in 2010. Based on the very short report of the study, 48 psychiatrists (71%) answered the questionnaire. Of the respondents, 96% had prescribed second-generation APs for off-label indications and most often the primary choice was quetiapine (94%). The most prescribed off-label indications were anxiety (89%) and sedation (79%), which we assume means treating conditions of overarousal (e.g. anxiety) and probably also problems of sleeping. Only 2% had prescribed AP for insomnia (19).

These results of Monasterio and McKean (19) are similar to our results when looking at the popularity of quetiapine and anxiety as an indication. Regarding insomnia, the results were very different compared to our study, so the question arises whether the respondents considered insomnia, when reporting sedation, as a reason for off-label prescription (19). The number of psychiatrists in our study was about twice the number in Monasterio and McKean (19). This kind of questionnaire survey on the subject has not been conducted much in the past, so our study is both nationally and internationally important.

A systematic literature review including a total of 77 studies concluded that quetiapine was the most often prescribed off-label AP among adults, while among children risperidone and aripiprazole were most frequently prescribed for off-label use (5). The reasons for off-label use of APs among children are somewhat different than those of adults. Children who are being prescribed APs off-label have had, for example, a diagnosis of ADHD (5). However, the evidence for treating symptoms of ADHD with APs is low (20), including two RCTs showing efficacy for risperidone compared to placebo in treatment of aggression in ADHD (21) and reduced ADHD symptoms with risperidone and methylphenidate, with a greater reduction of symptoms with risperidone than methylphenidate among children with both ADHD and intellectual disability (22).

In an international study by Hálfdánarson et al. (4) of 16 countries, involving data from millions of patients, it was also found that quetiapine was the most often prescribed AP across all age groups followed by risperidone and olanzapine. However, when looking at different age groups, variation occurred. Risperidone, quetiapine and aripiprazole were the most frequently prescribed APs among children. In adults, the three most commonly prescribed APs were quetiapine, olanzapine and risperidone (4). It is good to note that the results from Hálfdánarson et al. (4) apply to all AP use, not just off-label use.

In a large Chinese sample of patients discharged from psychiatric hospital, off-label prescription of APs was common (63% of the discharged patients), and the most common drugs were olanzapine and quetiapine (23).

Our findings support previous studies in that especially quetiapine is currently the most frequently used off-label antipsychotic medication followed by olanzapine, aripiprazole and risperidone. Our study did not ask separately what is prescribed for children and adolescents. Since quetiapine has been in previous studies, and in our study, the most commonly prescribed AP in off-label use, in discussion we focus on quetiapine. In addition, we focus on insomnia and anxiety, the most common condition for off-label use.

EFFECT OF ANTIPSYCHOTICS, ESPECIALLY QUETIAPINE ON INSOMNIA

There are some, but a relatively small number of studies on the efficacy of antipsychotics in insomnia. Especially studies on primary insomnia are only few (10,24). Mostly used APs for insomnia include quetiapine and olanzapine (10,24).

A review (13) on studies with quetiapine in patients with insomnia, including four trials (1379 patients in total) with unipolar or bipolar depression, showed statistically significant improvement in insomnia. The study questioned whether the insomnia improved because of improvement on depression or whether the insomnia improved regardless of the depression.

Individual studies show that quetiapine is effective in the treatment of insomnia in Parkinson's disease (25), drug-dependent patients (26), adolescent psychiatric patients (27), depression (28,29), breast cancer patients (30) and post-traumatic stress disorder (31). In these studies, insomnia decreased in 24-32% of the sample and quetiapine had a positive effect on the time to fall asleep, sleep length, restlessness and quality of sleep. Lower doses appeared to be better when comparing efficacy and disadvantages. However, it is noteworthy that only three of the studies with quetiapine were placebo-controlled and patient data differed widely between the studies, so no direct conclusions should be drawn (25-31).

The evidence for quetiapine in the treatment of primary insomnia is lacking, and there is only one RCT on primary insomnia (11), one on transient insomnia (32) and one open-label pilot study (12) on the topic. One RCT study involved 13 adults with primary insomnia, mostly women (11). Patients received either 25mg quetiapine or placebo for two weeks. No significant difference was found between groups. Side effects

were observed only in the quetiapine group (dry lips, dry tongue, daytime drowsiness) (11).

In an open-label pilot study, 18 adults with primary insomnia were first treated with 25mg quetiapine orally before going to sleep, and if needed increased to 50-75mg. Sleep parameters (total sleep time and sleep efficiency) improved after two weeks and kept improving at six weeks. The adverse effects reported most often were dry mouth and morning hangover effects (12).

Another RCT compared the effects of placebo, mirtazapine and quetiapine on transient insomnia (lasting less than a week) among 19 adults (32). Transient insomnia was simulated by disturbing sleep with acoustic stress (traffic noise) among persons without problems of sleep. There were three treatment sessions which all contained three consecutive nights: one night without medication, one night with 7.5mg mirtazapine and one night with 50mg quetiapine. Both quetiapine and mirtazapine increased sleep continuity and total sleep time compared to placebo, especially under acoustic stress. Disadvantages were fatigue after undisturbed sleep in both drugs. There were no differences between quetiapine and mirtazapine in efficacy or side effects (32).

The safety of quetiapine and other antipsychotics in treatment of insomnia has been raised (5,10) and will be discussed below. However, prolonged insomnia alone exposes to many somatic and mental disadvantages. Long-term poor sleep increases risk for depression and disability retirement (33). In addition, long-term follow-up studies have found an association between insomnia and several somatic and mental conditions: metabolic disorder, hypertension, type 2 diabetes, coronary artery disease, long-term pain conditions, susceptibility to infections and increased risk for suicide (34).

EFFECT OF ANTIPSYCHOTICS, ESPECIALLY QUETIAPINE ON ANXIETY

APs have shown efficacy in anxiety disorders in several trials. Based on a detailed review by Maglione et al. (10), moderate to high evidence for efficacy exists for quetiapine in the treatment of generalized anxiety disorder (GAD), risperidone (as augmentation) for obsessive-compulsive disorder and risperidone for post-traumatic stress disorder (10). For other disorders and APs, the evidence is either low or very low, or there are no trials (10).

The efficacy of quetiapine especially in generalized anxiety disorder (GAD) has been shown in several studies (10,35-38). According to Depping et al. (37) and Lalonde et al. (38), quetiapine monotherapy is effective in the treatment of GAD, even as effective as antidepressants (37,38). However, quetiapine has lower tolerability and more side effects compared to antidepressants, so it should be considered as a secondary treatment option.

Kreys et al. (35) showed that patients with GAD treated with quetiapine achieved more often remission compared to placebo, and its monotherapy was most effective. Dose size varied between 50mg and 300mg and did not matter in the study in terms of efficacy (35).

CONCERNS ABOUT AP OFF-LABEL USE, ESPECIALLY QUETIAPINE

Safety concerns have been presented as AP off-label prescriptions are on the increase despite limited research on evidence of safety and efficacy (5,10,13). In light of previous studies, the most common side effects of SGAP off-label use are weight gain, fatigue and drowsiness. Hyperglycemia, diabetes mellitus and dyslipidemia are also mentioned (10,39). It has also been reported that off-label AP use may be associated with suicidal ideation, but causality remains unsure (40). Among quetiapine users, weight gain and metabolic side effects are often reported as well as fatigue and sedation (5). Extrapyramidal symptoms are also associated with some APs (10).

For quetiapine, disadvantages have been reported even with low doses (41). In clinical trials in adults, a relatively low dose of quetiapine (ca. 117mg/d) significantly increased metabolic parameters (blood pressure, body weight, BMI, fasting glucose) after two years of use (42). Furthermore, in a study with quetiapine dosing up to 100mg, body weight increased at six and twelve months (43). Especially children and the elderly are sensitive to the side effects of low dose APs (44,45).

Previous clinical trials on the effects of APs in off-label use are relatively few and the trials have been selective: inclusion criteria have been strict which excludes patients who would be prescribed APs in real-world clinical practice. In addition, trials have been RCTs lasting only two to three months so long-term efficacy has not been studied. Previous trials have also not sufficiently elucidated the disadvantages in a long-term follow-up, and thus, for example, the metabolic disadvantages of prolonged use (from several months to years) are still unclear.

Concerns have also been raised regarding the potential misuse of quetiapine. In Australia, an increase in poisonings and mortality due to quetiapine between 2006-2016 has been reported (46). In a Finnish sample, quetiapine has been used as a suicide method especially among women (47).

CLINICAL AND PHARMACOLOGICAL PROFILE OF QUETIAPINE, THE MOST PRESCRIBED OFF-LABEL DRUG IN OUR STUDY

Scientists from AstraZeneca developed quetiapine in 1985, but it did not enter the market until 1997 (48). In Finland the marketing authorization was granted first for Seroquel in late 1999 (49). Official indications for quetiapine in Finland are schizophrenia, bipolar disorder and (for depot quetiapine) major depression (adjunctive therapy).

According to one study on national trends of AP use in the US between 1998-2002 (50), there was almost a three-fold increase in the number of visits relating to prescription of second-generation AP drugs. Also, significant change occurred in the rate of visits for SGAP agents as a percentage of visits for all AP medications. In 1998, 48% of visits were for SGAPs, but in 2002 the number had increased to 84% (50). One possible explanatory factor may be the entry of quetiapine to the market. While the overall usage of SGAPs has increased, so has the off-label use of quetiapine (51). For example, quetiapine off-label use alone accounted for 17% of the SGAP spend in New Zealand in 2010 (51).

The use of quetiapine in children and adolescents is usually off-label since official indications (under 18) are only for aripiprazole, periciazine, risperidone and ziprasidone (52). In Finland, quetiapine was the second most prescribed AP in children and adolescents under 18 between 2008-2015. In girls, quetiapine use increases significantly faster from the age of 14 than in boys, and increases 2.5-fold by age 17 compared to boys (52).

Quetiapine binds to several different receptors, mostly to H1 histamine receptor and α-1 adrenergic receptor but also with somewhat lower affinity to several serotonergic, muscarinic and dopaminergic receptors. The sedative and sleep promoting effect of quetiapine is thought to arise from its 5-HT2 and H1 receptor antagonist actions. H1 receptor antagonist actions also accounts for weight gain. Due to its several receptor effects, some people consider that quetiapine is not necessarily an AP at all, especially not in small doses. The quick sedative and anxiolytic effect may be the reason for its use in anxiety and insomnia.

According to one meta-analysis, which estimated D2 receptor occupancy for different APs, the maximum occupancy for quetiapine was 49.1%, which was the lowest of the APs studied and below the proposed therapeutic occupancy (65-80%) (53). Studies have shown that the disappearance of quetiapine from plasma is much faster than the decrease in occupancy of brain serotonin receptors (54). Better correlation has been found between D2 receptor dissociation and the plasma quetiapine half-life, but the correlation was still not very strong (54). Also, the relationship between quetiapine plasma concentrations at different dosages and clinical responses have been studied, but the results are contradictory: some studies showed no statistically significant association between plasma concentrations and clinical response (55,56), while some studies showed statistical difference (57,58). These results indicate the complex pharmacokinetics of quetiapine. To our knowledge, pharmacokinetic studies on very low doses (12.5-50mg) of quetiapine have not been published and the biological effects of very low doses of quetiapine remain unknown.

CLINICAL IMPLICATIONS

Off-label prescription of APs is relatively common in specialized mental healthcare, primary care and occupational healthcare. Due to limited evidence especially on long-term use of APs off-label, and due to even lack of evidence (regarding insomnia), AP off-label use should be based on very careful consideration after trying several other, evidence-based treatment options (59). The potential benefits and harms of AP off-label use should be weighted with each patient individually. In addition, there is a need for guidelines for the follow-up and monitoring, as well as discontinuation, of APs off-label. In clinical practice, careful follow-up and medication management of these patients is important (60). Especially weight, other metabolic side effects, and heart functioning, and daytime sedative effects should be followed up closely.

Psychiatrists are more likely to prescribe APs for off-label use than other doctors. This is likely to be related to psychiatrists having more knowledge and experience in prescribing medication for diseases for which APs have no official indication. On the other hand, psychiatrists also face more treatment-resistant patients for whom the use of off-label medication may be justified, but who on the other hand may have more comorbidities, co-medications and increased risk of potential side effects of concurrent medications. Guidelines on AP off-label use and monitoring of patients during AP use are needed for both primary care and psychiatric settings. This need is not limited to AP off-label use, but the need for clearer rules for off-label prescriptions in other fields of medicine is also acknowledged (61).

STRENGTHS AND LIMITATIONS OF OUR STUDY

One strength of our study is that this topic has not been studied in Finland before, neither has such a survey design been used much elsewhere in the world. There were respondents from several hospital districts from southern

Finland to Lapland. We also received responses from both those working in primary healthcare and those working in specialist healthcare. Furthermore, previous studies have focused more on psychiatrists. It is also very important to know the prescribing practices of primary care physicians, as a relatively large number of APs are prescribed by them.

The age and gender distribution of the physicians who participated in the study also represents quite well the age and gender distribution of all physicians in Finland. In our data, 31% of the respondents were men and 69% women, whereas the figures for the whole country are 39% and 61% (62). Similarly, in terms of age, those under 50 years accounted for 68% in our data and for the whole country the number is 60% (62).

We have few limitations in our study. The participation rate was low. The majority of respondents were from organizations in the Northern Ostrobothnia Hospital District, and the sample did not include respondents from the Hospital District of Helsinki and Uusimaa. Low participation rates are typical and increasing in physician-targeted surveys (63) due to the urgency and the workload of physicians. This may limit the generalizability of our study results.

In addition, it may be that those physicians who do prescribe APs were especially willing to answer, and doctors who do not prescribe APs did not participate. This may have had an effect on the result of frequency of off-label AP prescription and the true frequency may be somewhat smaller than in our sample. Also, our study did not cover all regions of Finland (such as the metropolitan area) so the results may have varied in these areas.

Some respondents may have thought that when asked for doses of medication, we meant any indication for the use of APs, not just off-label. This may have had an effect on psychiatrists' responses since they usually start APs for on-label indications. In terms of efficacy and disadvantages, we were only able to observe physicians' experiences, not the benefits and harms experienced by patients.

CONCLUSIONS

Off-label use of APs is common and a clinical reality in everyday patient work in general and occupational health practices. However, off-label use is minimally studied which is why it should be analysed in more detail to improve the quality of such use. Patients' symptoms such as anxiety and insomnia may decrease when using APs off-label. Despite this, future studies are warranted to scrutinize the possible benefits and side effects of off-label AP prescription and use. As the use of APs may be associated with metabolic side effects, patient weight, glucose and lipid values should be monitored regularly. It would also be important to evaluate the length of treatment with off-label APs during scheduled visits, and future studies on optimal length of off-label AP use are needed. Currently, off-label use seems to be often based on an individual and personal decision-making process. Personalized, tailored medication management is needed, especially in AP off-label use where guideline-concordant algorithms are vague and no formal clinical recommendations exist.

ACKNOWLEDGEMENTS

We would like to thank all the persons and organizations participating in this study. This work was supported by grants from the Academy of Finland (grant number 316563), and Oulu University Hospital funding (basic government funding for hospitals).

Authors

Jami Pentinlehto[1]
Marianne Haapea[1,2,3]
Lotta Ylitolonen[1]
Anni-Emilia Alakokkare[1,4]
Solja Niemelä [4,5]
Jouko Miettunen[1,3]
Matti Penttilä[1]
Hannu Koponen[6]
Jussi Seppälä[1,7]
Matti Isohanni[1]
Nina Rautio[1]
Erika Jääskeläinen[1,2,3]

[1] Center for Life Course Health Research, University of Oulu, Finland
[2] Department of Psychiatry, Oulu University Hospital, Oulu, Finland
[3] Medical Research Center, Oulu University Hospital and University of Oulu, Oulu, Finland
[4] Department of Psychiatry, University of Turku, Turku, Finland
[5] Addiction Psychiatry Unit, Turku University Hospital, Turku, Finland
[6] Psychiatry, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[7] Department of Mental and Substance Use Disorders, South Karelia Social and Health Care District, Lappeenranta, Finland

Corresponding author:

Erika Jääskeläinen
Center for Life Course Health Research, Medical Faculty
P.O. BOX 5000
90014 University of Oulu
Tel. +358 40 7191146
Email: *erika.jaaskelainen@oulu.fi*

Role of the funding source:

The funders had no role in the study design, data collection, data analysis, interpreting the results or the decision to publish the article.

References

1. European medicines agency. Glossary. keyword “off-label use”. https://www.ema.europa.eu/en/glossary/label-use. Read 04.05.2020.

2. Eguale T, Buckeridge DL, Winslade NE, Benedetti A, Hanley JA, Tamblyn R. *Drug, Patient, and Physician Characteristics Associated With Off-label Prescribing in Primary Care*. Arch Intern Med. 2012;172(10):781–788.

3. Radley DC, Finkelstein SN, Stafford RS. *Off-label Prescribing Among Office-Based Physicians*. Arch Intern Med. 2006;166(9):1021–1026.

4. Hálfdánarson Ó, Zoëga H, Aagaard L, Bernardo M, Brandt L, Fusté AC, Furu K, Garuolienė K, Hoffmann F, Huybrechts KF, Kalverdijk LJ, Kawakami K, Kieler H, Kinoshita T, Litchfield M, López SC, Machado-Alba JE, Machado-Duque ME, Mahesri M, Nishtala PS, Pearson SA, Reutfors J, Saastamoinen LK, Sato I, Schuiling-Veninga CCM, Shyu YC, Skurtveit S, Verdoux H, Wang LJ, Yahni CZ, Bachmann CJ. *International trends in antipsychotic use: A study in 16 countries, 2005-2014*. Eur Neuropsychopharmacol. 2017 Oct;27(10):1064-1076

5. Carton L, Cottencin O, Lapeyre-Mestre, Geofrroy P A, Favre J, Simon N, Bordet R, Rolland B. *Off-Label Prescribing of Antipsychotics in Adults, Children and Elderly Individuals: A Systematic Review of Recent Prescription Trends*. Curr Pharm Des 21: 3280-97

6. Bipolar disorder. Current Care Guidelines. Working group set by the Finnish Medical Society Duodecim, the Finnish Psychiatric Association and the Finnish Youth Psychiatric Association. Helsinki: The Finnish Medical Society Duodecim, 2013. (referred 18.06.2020). available online at: www.kaypahoito.fi

7. Schizophrenia. Current Care Guidelines. Working group set by the Finnish Medical Society Duodecim and the Finnish Psychiatric Association. Helsinki: The Finnish Medical Society Duodecim, 2020. (referred 18.06.2020). Available online at: www.kaypahoito.fi

8. Depression. Current Care Guidelines. Working group set by the Finnish Medical Society Duodecim and the Finnish Psychiatric Association. Helsinki: The Finnish Medical Society Duodecim, 2020. (referred 18.06.2020). Available online at: www.kaypahoito.fi

9. Tilastotietokanta Kelasto. Lääkkeet. Lääkekorvausten saajat ja reseptitiedot 2008-2019. www.kela.fi/tilastot. read 18.6.2020

10. Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, Wang Z, Timmer M, Sultzer D, Shekelle PG. *Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis.* JAMA. 2011 Sep 28;306(12):1359-69

11. Tassniyom K, Paholpak S, Tassniyom S, Kiewyoo J. *Quetiapine for primary insomnia: a double blind, randomized controlled trial*. J Med Assoc Thai. 2010 Jun;93(6):729-34

12. Wiegand MH, Landry F, Brückner T, Pohl C, Veselý Z, Jahn T. *Quetiapine in primary insomnia: a pilot study*. Psychopharmacology 196(2): 337-338

13. Anderson SL, Vande Griend JP. *Quetiapine for insomnia: A review of the literature*. Am J Health Syst Pharm. 2014 Mar 1;71(5):394-402.

14 Kela. Tietoa Kelasta. Tilastot. Tilastot aiheittain. Korvatut reseptit. www.kela.fi. read 15.08.2020

15 Pringsheim T, Gardner DM. *Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: a descriptive study*. CMAJ Open. 2014 Oct 1;2(4):E225-32

16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. *Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support*. J Biomed Inform. 2009;42:377-81

17. Harris PA, Taylor R, Minor BL ym. *The REDCap consortium: Building an international community of software partners*. J Biomed Inform 2019;95:103208.

18. Rautio N, Ylitolonen L, Haapea M, Huovinen H, Alakokkare A-E, Niemelä S, Miettunen J, Penttilä M, Koponen H, Seppälä J, Isohanni M, Jääskeläinen E. *Kysely Lääkäreille. Psykoosilääkkeiden off label -määräämisen käytännöt*. Suomen Lääkärilehti 2021, 35(76)

19. Monasterio E & McKean A. *Off-label use of atypical antipsychotic medications in Canterbury, New Zealand*. The New Zealand medical journal, 2011, 124: 24-9.

20. Maglione M, Ruelaz Maher A, Hu J, Wang Z, Shanman R, Shekelle PG, Roth B, Hilton L, Suttorp MJ, Ewing BA, Motala A, Perry T. *Off-Label Use of Atypical Antipsychotics: An Update*. Comparative Effectiveness Review No. 43. (Prepared by the Southern California Evidence-based Practice Center under Contract No. HHSA290-2007-10062- 1.) Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

21. Armenteros JL, Lewis JE, Davalos M. *Risperidone augmentation for treatment- resistant aggression in attention- deficit/ hyperactivity disorder: a placebo- controlled pilot study*. J Am Acad Child Adolesc Psychiatry. 2007;46(5):558- 65.

22. Correia Filho AG, Bodanese R, Silva TL, Alvares JP, Aman M, Rohde LA. *Comparison of risperidone and methylphenidate for reducing ADHD symptoms in children and adolescents with moderate mental retardation*. J Am Acad Child Adolesc Psychiatry. 2005;44(8):748- 55.

23. Wang J, Jiang F, Yang Y, Zhang Y, Liu Z, Qin X, Tao X, Liu T, Liu Y, Tang YL, Liu H, Cotes RO. *Off-label use of antipsychotic medications in psychiatric inpatients in China: a national real-world survey*. BMC Psychiatry. 2021 Jul 27;21(1):375.

24. Atkin T, Comai S, Gobbi G. *Drugs for Insomnia beyond Benzodiazepines*. Pharmacological Reviews April 1, 2018, 70 (2) 197-245

25. Juri C, Chaná P, Tapia J, Kunstmann C, Parrao T. *Quetiapine for Insomnia in Parkinson Disease: Results from an Open-Label Trial*. Clinical Neuropharmacology 28(4): 185-187

26. Terán A, Majadas S, Galan J. *Quetiapine in the Treatment of Sleep Disturbances Associated with Addictive Conditions: A Retrospective Study*. Substance Use & Misuse 43(14): 2169-2171.

27. Al-Dharer Z, Kapoor S, Saito E, Krakower S, David L, Ake T ym. *Activating and Tranquilizing Effects of First-Time Treatment with Aripiprazole, Olanzapine, Quetiapine, and Risperidone in Youth*. Journal of Child and Adolescent Psychopharmacology 26(5): 458-470

28. Bauer M, McIntyre RS, Szamosi J, Eriksson H. *Evaluation of adjunct extended release quetiapine fumarate on sleep disturbances and quality in patients with major depressive disorder and an inadequate response to on-going antidepressant therapy*. The International Journal of Neuropsychopharmacology 16(8): 1755-1765

29. Trivedi MH, Bandelow B, Demyttenaere K, Papakostas GI, Szamosi J, Earley W, Eriksson H. *Evaluation of the effects of extended release quetiapine fumarate monotherapy on sleep disturbance in patients with major depressive disorder: a pooled analysis of four randomized acute studies*. Int J Neuropsychopharmacol. 2013 Sep;16(8):1733-44

30. Pasquini M, Speca A, Biondi M. *Quetiapine for Tamoxifen-Induced Insomnia in Women with Breast Cancer*. Psychosomatics 50(2): 159-161.

31. Villarreal G, Hamner MB, Cañive JM, Robert S, Calais LA, Durklaski V, Zhai Y, Qualls C. *Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial*. Am J Psychiatry. 2016 Dec 1;173(12):1205-1212.

32. Karsten J, Hagenauw LA, Kamphuis J, Lancel M. *Low doses of mirtazapine or quetiapine for transient insomnia: A randomised, double-blind, cross-over, placebo-controlled trial*. J Psychopharmacol. 2017 Mar;31(3):327-337

33. Paunio, T., Korhonen, T., Hublin, C., Partinen, M., Koskenvuo, K., Koskenvuo, M., & Kaprio, J. *Poor sleep predicts symptoms of depression and disability retirement due to depression*. Journal of Affective Disorders, 172, 381–389.

34. Kryger MH, Roth T, Dement WC. *Principles and practice of sleep medicine*. 5. edition. St Louis, MI: Elsevier, 2010

35. Kreys TJ, Phan SV. *A literature review of quetiapine for generalized anxiety disorder*. Pharmacotherapy. 2015 Feb;35(2):175-88.

36. Maneeton N, Maneeton B, Woottiluk P, Likhitsathian S, Suttajit S, Boonyanaruthee V, Srisurapanont M. *Quetiapine monotherapy in acute treatment of generalized anxiety disorder: a systematic review and meta-analysis of randomized controlled trials*. Drug Des Devel Ther. 2016 Jan 12;10:259-76

37. Depping AM, Komossa K, Kissling W, Leucht S. *Second-generation antipsychotics for anxiety disorders*. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD008120

38. LaLonde CD, Van Lieshout RJ. *Treating generalized anxiety disorder with second generation antipsychotics: a systematic review and meta-analysis*. J Clin Psychopharmacol. 2011 Jun;31(3):326-33

39. Scheltema Beduin A, de Haan L. *Off-label second generation antipsychotics for impulse regulation disorders: a review*. Psychopharmacol Bull. 2010;43(3):45-81

40. Rissanen, I., Jääskeläinen, E., Isohanni, M., Koponen, H., Joukamaa, M., Alaräisänen, A. and Miettunen, J. (2012), *Use of antipsychotic medication and suicidality—the Northern Finland Birth Cohort 1966*. Hum. Psychopharmacol Clin Exp, 27: 476-485

41. Brett J. *Concerns about quetiapine*. Aust Prescr 2015;38(3):95-7.

42. Carr CN, Lopchuk S, Beckman ME. *Evaluation of the use of low-dose quetiapine and the risk of metabolic consequences: A retrospective review*. Ment Health Clin 2016;6(6):308-13

43. Williams SG, Alinejad NA, Williams JA, Cruess DF. *Statistically significant increase in weight caused by low-dose quetiapine*. Pharmacotherapy 2010;30(10):1011-5

44. Saastamoinen L, Autti-Rämö I, Tuulio-Hendriksson A, Sourander A. *Lasten ja nuorten psykoosilääkkeiden käyttö kasvussa*. Suomal Lääkäril 2017;72:575-9

45. Jalava S, Pohjanoksa-Mäntylä M, Puustinen J, Airaksinen M, Dimitrow M. *Psykoosilääkkeiden käyttö iäkkäillä: järjestelmällinen katsaus*. Suomal Lääkäril 2018;73(33):1743-9a

46. Lee J, Pilgrim J, Gerostamoulos D, Robinson J, Wong A. *Increasing rates of quetiapine overdose, misuse, and mortality in Victoria, Australia*. Drug Alcohol Depend. 2018 Jun 1;187:95-99.

47. Mainio A, Kuusisto L, Hakko H, Riipinen P. *Antipsychotics as a method of suicide: population based follow-up study of suicide in Northern Finland*. Nord J Psychiatry. 2020 Nov 20:1-5.

48. Riedel M, Müller N, Strassnig M, Spellmann I, Severus E, Möller HJ. *Quetiapine in the treatment of schizophrenia and related disorders*. Neuropsychiatr Dis Treat. 2007;3(2):219-235.

49. Fimea. Ihmisille tarkoitettujen lääkevalmisteiden valmisteyhteenvedot (Summary of Product Characteristics, SPC. http://spc.fimea.fi/. read 05.11.2020

50. Rajender R. Aparasu, Vinod Bhatara & Sanjay Gupta. *U.S. National Trends in the Use of Antipsychotics During Office Visits, 1998–2002*. Annals of Clinical Psychiatry, 2005. 17:3, 147-152

51. McKean, A., Monasterio, E. *Off-Label Use of Atypical Antipsychotics*. CNS Drugs 26, 383–390 (2012)

52. Saastamoinen LK, Autti-Rämö I, Tuulio-Henriksson A, Sourander A. *Lasten ja nuorten psykoosilääkkeiden käyttö kasvussa*. Lääkärilehti, 9/2017 vsk 72 s. 575 – 579

53. Lako IM, van den Heuvel ER, Knegtering H, Bruggeman R, Taxis K. *Estimating dopamine D_2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis*. J Clin Psychopharmacol. 2013 Oct;33(5):675-81.

54. Mauri MC, Volonteri LS, Colasanti A, Fiorentini A, De Gaspari IF, Bareggi SR. *Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response*. Clin Pharmacokinet. 2007;46(5):359-88

55. Fabre LF Jr, Arvanitis L, Pultz J, Jones VM, Malick JB, Slotnick VB. *ICI 204,636, a novel, atypical antipsychotic: early indication of safety and efficacy in patients with chronic and subchronic schizophrenia*. Clin Ther. 1995 May-Jun;17(3):366-78

56. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG. *Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo*. Seroquel Study Group. Arch Gen Psychiatry. 1997 Jun;54(6):549-57

57. Maud, MC, Fiorentini, Alessio & Volonteri, LS & Beraldo, S & Dell'Osso, Bernardo & Valli, Isabel & Pirola, R & Bareggi, SR. *Quetiapine in acute psychosis and personality disorders during hospitalization: Assessment of a therapeutic*. Eur Neuropsychopharmacol. 14. S283-S284.

58. Gefvert O, Bergström M, Långström B, Lundberg T, Lindström L, Yates R. *Time course of central nervous dopamine-D2 and 5-HT2 receptor blockade and plasma drug concentrations after discontinuation of quetiapine (Seroquel) in patients with schizophrenia*. Psychopharmacology (Berl). 1998 Jan;135(2):119-26

59. Rios P, Cardoso R, Morra D, Nincic V, Goodarzi Z, Farah B, Harricharan S, Morin CM, Leech J, Straus SE, Tricco AC. *Comparative effectiveness and safety of pharmacological and non-pharmacological interventions for insomnia: an overview of reviews*. Syst Rev. 2019 Nov 15;8(1):281.

60. Isohanni M, Jääskeläinen E, Miller B ym, *Medication management of antipsychotic treatment in schizophrenia—a narrative review*. Human Psychopharmacology 2020

61. Drenska M, Naseva E, Getov IN. *The knowledge and experience with the off-label use – results of a survey.* Pharmacia 66(4):2017-221.

62. Lääkäriliitto. Lääkärilaskuri https://www.laakariliitto.fi/laakariliitto/tutkimus/laakarityovoima/laakarilaskuri/. Read 12.1.2021

63. Weaver L, Beebe TJ, Rockwood T. *The impact of survey mode on the response rate in a survey of the factors that influence Minnesota physicians' disclosure practices.* BMC Med Res Methodol. 2019 Apr 2;19(1):73.

Attachment 1. The survey template

1. How old are you?:
   b. under 31
   c. 31-40
   d. 41-50
   e. 51-60
   f. 61-70
   g. over 70 years

2. Your gender?:
   a. woman
   b. man
   c. other

3. Are you?:
   a. medical student
   b. physician
   c. specializing physician or specialist

   If you are specializing or a specialist, what is your specialization?

4. How many years have you worked as a physician?:
   a. I am a medical student
   b. under 5 years
   c. 5-10
   d. 11-20
   e. 21-30
   f. over 30 years

5. Where do you work? (you can choose multiple options)
   a. health centre/station
   b. ward of a health centre
   c. maternity or child welfare clinic
   d. occupational health service
   e. outpatient unit of mental health services
   f. substance abuse services
   g. outpatient clinic of a psychiatric hospital
   h. ward of a psychiatric hospital
   i. private medical centre
   j. somewhere else, where?

6. In which hospital district do you work?
   a. South Karelia social and health district
   b. The hospital district of Helsinki and Uusimaa
   c. Lapland hospital district
   d. Pirkanmaa hospital district

e. Northern Ostrobothnia hospital district
f. North Savo hospital district
g. Southwest Finland hospital district

7. On average, how often do you prescribe antipsychotics?
   a. daily
   b. a few times a week
   c. about once a week
   d. every 1-2 weeks
   e. about once a month
   f. rarely
   g. I do not prescribe antipsychotics at all

8. To what aged patients do you usually prescribe antipsychotics?
   a. under 13 years
   b. 13-18 years
   c. 18-64 years
   d. 65-74 years
   e. over 74 years

9. What are the most common medical conditions for which you are prescribing antipsychotics? (you can choose multiple options)
   a. psychotic disorders
   b. bipolar disorder
   c. aggression in dementia
   d. other behavioural disorders regardless of age
   e. depression
   f. insomnia
   g. anxiety
   h. borderline personality
   i. neuropsychiatric disorders (e.g. ADHD)
   j. substance abuse disorder
   k. something else

   If you answered something else, what?

10. Have you prescribed antipsychotics for diseases or symptoms for which antipsychotics have no official indication? (Official indications: psychosis, bipolar disorder, aggression in dementia and behavioural disorders (risperidone only), adjunctive therapy for major depression (long-acting quetiapine only). Most of antipsychotic use for persons under 18 years of age is without official indication
    a. no
    b. yes

11. On average, how often do you prescribe antipsychotics for an illness or symptoms for which there is no official indication?
    a. daily
    b. a few times a week
    c. about once a week
    d. every 1-2 weeks
    e. about once a month

f. rarely
g. I do not start antipsychotics at all without an official indication

12. On average, how often do you renew an antipsychotic prescription for an illness or symptoms for which there is no official indication?
a. daily
b. a few times a week
c. about once a week
d. every 1-2 weeks
e. about once a month
f. rarely
g. I do not renew antipsychotic prescriptions at all without an official indication

13. Do you consult a psychiatrist, geriatrician, adolescent psychiatrist or child psychiatrist before prescribing antipsychotics without an official indication?
a. no, I do not consult
b. yes, I consult always or almost always
c. yes, I consult sometimes
d. I am psychiatrist, geriatrician, adolescent psychiatrist or child psychiatrist or specializing in these

14. For what symptom or illness do you most commonly prescribe an antipsychotic when the drug has no official indication for it? (you can choose multiple options)
a. anxiety
b. insomnia
c. unipolar non-psychotic depression (when prescribing something else than long-acting quetiapine, which is the only second-generation antipsychotic with an indication for non-psychotic depression)
d. neuropsychiatric disorders (e.g. ADHD)
e. borderline personality
f. substance abuse disorders
g. aggression in dementia (when prescribing something else than risperidone, which is the only second-generation antipsychotic with an indication for aggression in dementia)
h. for something else

If you answered something else, what?

15. Have patients whom you start antipsychotics without an official indication usually had previous use of other medications for these symptoms? (For example, a person with insomnia may have previously used melatonin or mirtazapine.)
a. no
b. yes

If you answered yes, which medications in general? (you can choose multiple options):
i. melatonin
ii. sleeping pill zolpidem or zopiclone
iii. a sedative such as oxazepam, diazepam
iv. mirtazapine for the treatment of insomnia
v. an antidepressant for the treatment of depression or anxiety
vi. antipsychotic
vii. something else

If you answered something else, what?

16. What antipsychotics do you usually prescribe for use without an official indication?
    a. quetiapine
    b. risperidone
    c. olanzapine
    d. aripiprazole
    e. perphenazine
    f. something else

In the following sections, you can mark the most typical daily dose for the medicines you usually prescribe. You can also indicate the dose range if you want:

quetiapine _____
risperidone _____
olanzapine_____
aripiprazole _____
perphenazine _____
something else, what? _____

17. How long do you usually instruct a patient to use an antipsychotic without an official indication?
    a. up to a few weeks
    b. 1-3 months
    c. 3-6 months
    d. 6-12 months
    e. over 12 months
    f. I do not give instructions on the length of treatment

18. Do you monitor the clinical status of these patients?
    a. I do not monitor
    b. yes I do
    c. If you do monitor, what parametres do you follow (you can choose multiple options):
        i. change in symptoms
        ii. change in functional capacity
        iii. metabolic values
        iv. other somatic condition
        v. side effects of medication
        vi. something else

        If you answered something else, what?

19. What benefits have you noticed from using antipsychotics without an official indication? (you can choose multiple options)
    a. mood rising
    b. mood stabilizing
    c. relief of anxiety
    d. decrease of insomnia
    e. relief of agitation or aggression
    f. improvement of functional capacity
    g. something else

    If you answered something else, what?

20. What disadvantages have you noticed in the use of antipsychotics without an official indication? (you can choose multiple options)
    a. fatigue or excessive sleepiness
    b. extrapyramidal symptoms
    c. mood decreasing
    d. anhedonia (inability to feel pleasure)
    e. weight gain
    f. rise in cholesterol levels
    g. effects on blood pressure or heart rate
    h. dry mouth
    i. something else

    If you answered something else, what?

21. In your experience, is there more benefit or harm from using antipsychotics without an official indication?
    a. more benefits
    b. more harm
    c. equally harms and benefits

    If you want, you can tell more about your answer here:

22. Do you sometimes prescribe two or more antipsychotics at the same time for a condition for which there is no official indication?
    a. no
    b. yes

23. Which one do you find easier?
    a. initiating antipsychotic medication on a patient without an official indication
    b. discontinuation of an antipsychotic from a patient without an official indication
    c. I can not answer

Would you like to tell more about this topic? You can also write comments about the questionnaire here: