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## Somatic monitoring of patients with mood and anxiety disorders

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## MEDICATION DISCREPANCIES AT OUTPATIENT DEPARTMENTS FOR MOOD AND ANXIETY DISORDERS IN THE NETHERLANDS: RISKS AND CLINICAL RELEVANCE

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## ABSTRACT

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### Objective

To identify discrepancies between actual drug use by outpatients with mood and anxiety disorders and medication overviews from health care providers as well as to investigate the clinical relevance of those discrepancies.

### Methods

A cross-sectional study in adults visiting one of four participating outpatient departments for mood and anxiety disorders was conducted between March and November 2014. *DSM-5* criteria were used to assign the psychiatric diagnosis. The primary outcome was the number of discrepancies between the actual medication use, as determined by medication reconciliation with the patient, and the medication overview from the outpatient department, general practitioner, and community pharmacy. Our secondary outcome was the clinical relevance of discrepancies, as assessed by an expert panel that reviewed all discrepancies for their potential to cause patient harm.

### Results

Of 367 patients included, 94.8% had at least one discrepancy in the medication overview from the outpatient department. A mean of 3.9 discrepancies existed per patient. Most discrepancies (74.5%) related to omitted drugs (drugs taken regularly by patients but absent from the medication overview). Of all discrepancies at the outpatient departments, 22.7% had the potential to cause moderate to severe discomfort or clinical deterioration, affecting 49.3% of the patients. Both total number and number of clinically relevant discrepancies were lower in medication overviews from general practitioners and pharmacies.

### Conclusion

Patients from outpatient departments for mood and anxiety disorders may be at substantial risk for medication discrepancies that are often clinically relevant. Medication reconciliation at mental health care outpatient departments is in need of improvement.

## INTRODUCTION

Psychiatric patients commonly use combinations of psychiatric and general medical drugs for their mental illness and the frequently occurring somatic comorbidities or side effects of psychiatric medication.<sup>1,2</sup> Various prescribers from different health care institutions, including general practitioners, prescribe these drugs. In addition, patients may use non-prescription drugs, mostly unadvised and unsupervised by health care professionals.

To correctly evaluate a patient's clinical status and allow adequate adjustment of pharmacotherapeutic treatment, clinicians need to have a complete medication overview. This overview is obtained by a process called medication reconciliation in which the actual medication use is determined. Despite reliable community pharmacy records in the Netherlands, previous research has shown that patient counselling is a crucial part of medication reconciliation to create a complete overview of the actual medication use by the patient.<sup>3,4</sup> Medication reconciliation through combination of pharmacy records and patient counselling results in an up-to-date and complete medication overview including current medication use and all medication allergies or intolerances.

Most research on quality of medication reconciliation has been conducted in hospital settings and reported discrepant medication overviews in 34%–95% of patients.<sup>5,6</sup> An incomplete or erroneous medication overview may lead to failure to detect cause and consequence of side effects and somatic complications, prescribing errors, and iatrogenic harm. However, little is known about the clinical importance of medication discrepancies. One systematic review<sup>5</sup> examining the clinical relevance of such errors after hospital admission showed that approximately 11%–59% of the medication discrepancies were clinically important. However, in patients admitted to a geriatric psychiatric clinic, 82% of all discrepancies were clinically relevant.<sup>6</sup> To our knowledge, there are no studies reporting medication discrepancies and their clinical relevance in psychiatric outpatients.

Therefore, we addressed two issues. First, we examined whether psychiatrists have an up-to-date medication overview available for treatment evaluation when their patients visit them. Second, we assessed whether incomplete and erroneous medication overviews at psychiatric outpatient clinics are clinically relevant. We investigated outpatients with mood and anxiety disorders in the northern part of the Netherlands, aiming to identify discrepancies between the medication overview available at psychiatry outpatient departments and the actual drug use as well as to investigate their clinical relevance. For comparison, we also assessed discrepancies in the medication overviews from the general practitioners and community pharmacies of the same patients.

## METHODS

### Design and setting

We used a cross-sectional design to assess discrepancies between the reconciled medication use and the medication overview from different health care providers.

The study was conducted at four outpatient departments for mood and anxiety disorders in the northern part of the Netherlands: three from two large secondary mental health care institutions and one from an academic hospital.

In the Netherlands, it is mandatory to have a complete and up-to-date medication overview (including drugs prescribed by other physicians) available for clinical decision making whenever a patient contacts a prescriber. The prescriber is responsible for updating this information through reconciliation with the patient. This information is recorded in the electronic medical record (EMR) of the patient.

### Study population

We included patients 18 years or older who had visited the participating outpatient department at least once. The latter criterion ensured that the treating mental health care provider had had the opportunity to certify information regarding medication use after the first visit.

We consecutively recruited patients when visiting the outpatient departments between March and November 2014. We obtained written informed consent after complete verbal and written description of the study. An independent medical ethics committee (rTPO Leeuwarden, the Netherlands) waived formal review and approval of the study protocol since participants were not subject to interventions nor were they required to follow rules of behaviour for this study.

We used the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), criteria for psychiatric classification of participants.

### Outcomes

Primary outcomes were the percentage of patients with at least one discrepancy and the number and type of discrepancies between the reconciled medication use and the medication use according to the medication overview from the mental health care institution, general practitioner, and community pharmacy on the day of inclusion. Discrepancies provide information regarding the actual medication use by the patient but not necessarily regarding the correct medication use in a pharmacologic sense.

Secondary outcomes were the clinical relevance of the discrepancies and the need for intervention as a consequence of the discrepancies.

### Discrepancy assessment and classification

We determined actual medication use on the inclusion date by medication reconciliation with the patient immediately after the consult with a mental health care provider. In concordance with other studies<sup>3,4</sup>, we considered medication reconciliation combining recorded (pharmacy records) and patient-reported information the gold standard for determining the actual medication use by the patient. If the patient-reported medication use differed from the pharmacy records, we used the patient-reported information to

assess the actual drug use by the patient. This actual medication use might be discrepant from the drug use the psychiatrist expected.

We defined a discrepancy as any difference between the reconciled medication use or allergies/intolerances and the medication overview from the EMR at the outpatient department, the general practitioner, or the community pharmacy.

We considered all drugs approved by the Dutch Medicines Evaluation Board or European Medicines Evaluation Authority. Drugs with a unique active ingredient, strength, or route of administration were considered separate drugs. To prevent overestimation of discrepancies, we counted a maximum of one discrepancy per actual drug or allergy/intolerance instead of all differences (e.g., total daily dose and route of administration). In addition, we used a margin of 28 days around the theoretical starting and end dates of a drug on the medication overviews from the health care providers in which period the drug was considered to be still in use.<sup>7</sup> For example, when a patient's lithium refill had theoretically ended fourteen days before the inclusion date, but the patient reported to still use lithium, we recorded no discrepancy if the daily dose and route of administration matched as well. However, we would have recorded a discrepancy if the refill had ended more than 28 days before the inclusion date.

We subsequently classified discrepancies as one of five types: extra drug, omitted drug, difference in total daily dose, difference in route of administration, or difference in allergy or intolerance. Whenever we identified differences in both dose and route of administration for 1 drug, we classified the discrepancy as a difference in total daily dose.

Discrepancies do not necessarily reflect clinically relevant issues. To overcome this limitation to our design, we evaluated the clinical relevance of discrepancies. An expert panel consisting of a hospital pharmacist and clinical pharmacologist (A.J.R.) and a psychiatrist (F.W.W.) independently classified each discrepancy in one of three classes for its potential to cause patient harm, as adopted from Cornish et al.<sup>8</sup> Class 1 discrepancies are those unlikely to cause patient discomfort or clinical deterioration, while class 2 and 3 discrepancies could potentially result in respectively moderate and severe discomfort or clinical deterioration. In addition, only for discrepancies at the mental health care institutions, the expert panel evaluated the need for intervention in order to prevent or alleviate any possible harm as a consequence of the discrepancy. The expert panel classified suggested interventions in six categories: consider measuring a somatic parameter, prescribing an extra drug, stopping a current drug, changing a current drug (without altering the active ingredient [e.g., a change in dose or route of administration]), replacing a current drug (by another drug within the same therapeutic class [e.g., one antidepressant by another antidepressant or one  $\beta$ -blocking agent by another  $\beta$ -blocking agent]), or re-evaluating total medication use.

The two experts resolved all disagreements in classifications by discussion.

## Statistical analysis

Descriptive and statistical analysis was completed using Excel 2013 (Microsoft, Redmond, Washington) and IBM SPSS (version 20 for Windows; IBM Corp, Armonk, New York).

We investigated the number of discrepancies and the percentage of clinically relevant discrepancies (classes 2 and 3) for differences per setting (both the four outpatient departments separately and the academic/community departments) in univariate linear regression models, using a  $p < 0.05$  significance level.

Interrater reliability of the expert panel members for judging the clinical relevance and the need for intervention was analysed using a weighted  $\kappa$  score with squared weights<sup>9</sup> and a Cohen  $\kappa$  score, respectively.

## RESULTS

### Participants

We asked 495 consecutively eligible patients to participate in the study at the four locations. Of these patients, 370 gave written informed consent (104, 103, 102, and 61 out of 131, 142, 143, and 79 patients at the four locations, respectively). Reasons for not participating

Table 1. Characteristics of the study population<sup>a</sup>

Characteristic	Value
Female, n (%)	228 (62.1%)
Age, mean $\pm$ SD, years	44.3 $\pm$ 12.4
Educational level, n (%)	
No education	1 (0.3%)
Primary school	17 (4.6%)
Preparatory vocational secondary education	83 (22.6%)
Secondary vocational education	145 (39.5%)
Senior general secondary education or pre-university education	39 (10.6%)
Higher professional education	69 (18.8%)
Academic higher education	12 (3.3%)
Unknown	1 (0.3%)
Length of outpatient treatment, mean $\pm$ SD, years	1.5 $\pm$ 2.3
Primary psychiatric diagnosis (DSM-5 diagnostic criteria), n (%)	
Bipolar or related disorder	49 (13.4%)
Depressive disorder	141 (38.4%)
Anxiety disorder	59 (16.1%)
Other psychiatric disorder	84 (22.9%)
Not yet diagnosed	31 (8.4%)
Unknown	3 (0.8%)
Number of drugs (psychotropic and somatic drugs), mean $\pm$ SD	4.6 $\pm$ 3.0

<sup>a</sup> Since outcomes did not differ statistically per setting, patient characteristics are presented for the total population (n=367). DSM Diagnostic and Statistical Manual of Mental Disorders.

included “no time” and “privacy.” We subsequently excluded two patients from analysis because they had withdrawn consent and one because medication reconciliation could not be achieved due to “no show” of the patient. Since outcomes did not statistically differ per setting, we present patient characteristics for the total population (n = 367) in Table 1. As expected for mood and anxiety disorders, female participants were overrepresented (62.1%). Participants mostly had a low level of education and used a mean of 4.6 drugs.

**Number and type of discrepancies**

We found at least one discrepancy in the medication overview of the outpatient departments for mood and anxiety disorders in 348 patients (94.8%), with a mean±SD of 3.9±2.8 discrepancies per patient (Figure 1). Discrepancy numbers did not differ significantly between outpatient departments (p=0.362) or between academic and community settings (p=0.773). In the medication overviews of the general practitioners and pharmacies, we found at least one discrepancy in 90.2% and 85.8% of the patients, respectively, with corresponding mean±SD values of 2.9±2.1 and 2.2±1.7 discrepancies per patient.

Figure 1 shows numbers and types of discrepancies per patient per health care provider. Most discrepancies for each health care provider were omitted drugs, i.e., drugs the patient was regularly taking but that were absent from the health care provider’s records (74.5%, 65.4%, and 63.4% for the outpatient departments, general practitioners, and

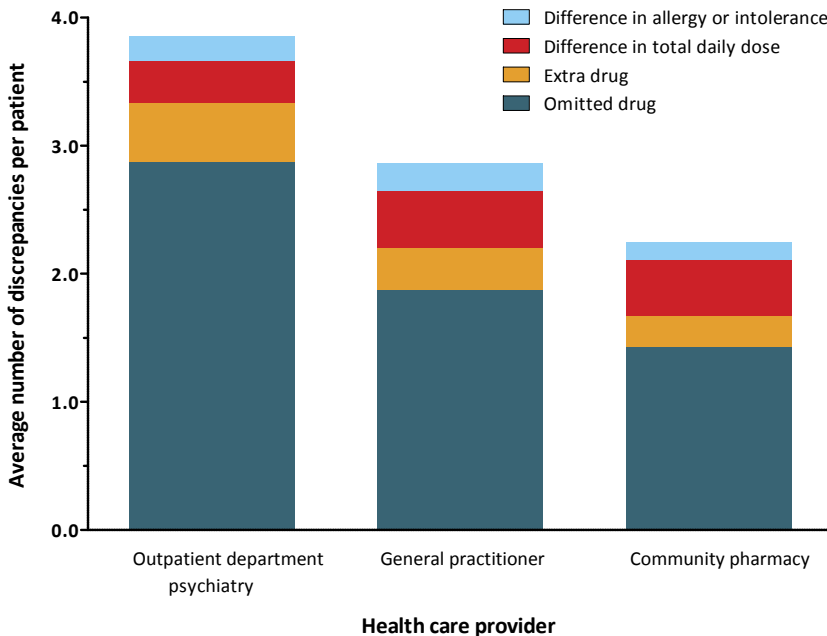


Figure 1. Number and type of discrepancies per health care provider. Data are presented for the total population (n=367), as the number of discrepancies did not significantly differ between the four outpatient departments (p=0.362) nor between academic and community settings (p=0.773). No differences in route of administration were found.



pharmacies, respectively). Discrepancies regarding medication (allergies or intolerances excluded) mostly concerned paracetamol (Anatomical Therapeutic Chemical [ATC] code N02BE; 15.1%), anxiolytic benzodiazepine derivatives (N05BA; 6.4%), and proton pump inhibitors (A02BC; 4.9%) at the outpatient departments; paracetamol (20.8%), anxiolytic benzodiazepine derivatives (7.3%), and propionic acid derivatives (M01AE, e.g., ibuprofen; 6.1%) at the general practitioners; and paracetamol (25.9%), propionic acid derivatives (7.5%), and anxiolytic benzodiazepine derivatives (6.5%) at the pharmacies.

### Clinical relevance of discrepancies

Figure 2 shows the classification of the discrepancies for their potential to cause patient harm, as assessed by the expert panel. The interrater reliability for judging the clinical relevance (classes 1–3) was moderate (weighted  $\kappa=0.58$ ; 95%CI 0.53–0.63). Of the discrepancies at the outpatient departments, 77.2% were unlikely to cause harm (class 1), while 19.9% and 2.8% of the discrepancies were found to potentially cause moderate (class 2) or severe (class 3) discomfort or clinical deterioration, respectively.

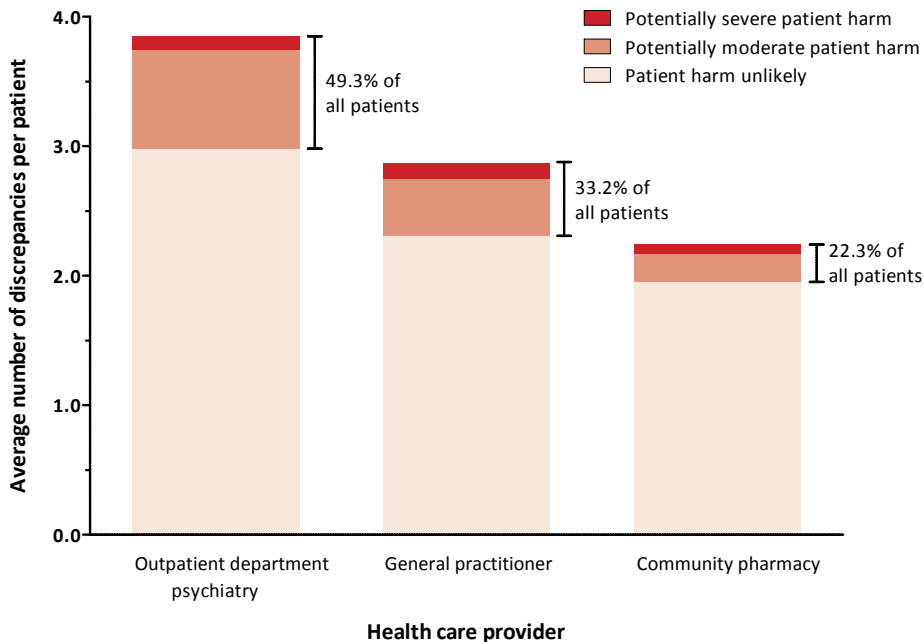


Figure 2. Clinical relevance of discrepancies per health care provider. Discrepancies were classified by the expert panel as unlikely to cause patient harm, having the potential to cause moderate patient harm, and having the potential to cause severe patient harm. Data are presented for the total population ( $n=367$ ), as the percentage of clinically relevant discrepancies did not significantly differ between the four outpatient departments ( $p=0.440$ ) or between academic and community settings ( $p=0.379$ ). The numbers next to the braces indicate the percentage of all patients affected by at least one discrepancy with the potential to cause moderate to severe patient harm.

Table 2. Examples of classification of discrepancies at mental health care outpatient departments

Primary DSM-5 diagnosis	Medication use <sup>a</sup>	Description of discrepancy	Type of discrepancy	Clinical relevance class <sup>b</sup>	Intervention necessary?	Type of intervention (supplement)
Anxiety disorder	Citalopram, mirtazapine	Patient was taking ibuprofen, 400 mg as needed about four times a month, which was absent from the medication overview of the mental health care department	Omitted drug	1	No	N/A
Depressive disorder	Paroxetine, mirtazapine, zopiclon, citalopram	Patient reported taking paroxetine, 20 mg/day, while the medication overview of the mental health care department stated paroxetine 10 mg/day	Difference in dose	1	No	N/A
Depressive disorder	Venlafaxine, fluticasone nasal spray, ciclosonide inhaler, formoterol inhaler, lithium, lynestrenol, hydrochlorothiazide, lisinopril, montelukast, salbutamol	Patient was taking hydrochlorothiazide, 12.5 mg/day, which was absent from the medication overview of the mental health care institution	Omitted drug	2	Yes	Consider measuring a somatic parameter (sodium level for diagnosis of possible SIADH as an adverse effect of the co-use of hydrochlorothiazide and venlafaxine)
Depressive disorder	Ibuprofen, temazepam, venlafaxine, simvastatin, hydrochlorothiazide, mirtazapine, salmeterol/fluticasone propionate inhaler, desloratadine, lisinopril, dextran 70/hypromellose eye drops, polyacrylic acid eye gel	Esomeprazole, 20 mg/day, was present on the medication overview of the mental health care institution, but the patient was not taking it	Extra drug	2	Yes	Consider prescribing an extra drug (restart esomeprazole for prevention of gastric complications as a possible adverse effect of the co-use of ibuprofen and venlafaxine)

Table 2. (continued)

Primary DSM-5 diagnosis	Medication use <sup>a</sup>	Description of discrepancy	Type of discrepancy	Clinical relevance class <sup>b</sup>	Intervention necessary?	Type of intervention (supplement)
Bipolar or related disorder	Levothyroxine, valproic acid, zuclopenthixol	Patient was taking valproic acid, 2000 mg/day, which was absent from the medication overview of the mental health care institution	Omitted drug	3	Yes	Consider measuring a somatic parameter (valproic acid serum concentration, as this may be not monitored in this patient and out-of-range valproic acid serum concentrations should be avoided because of the risks of undertreatment (too low) and toxicity (too high))
Depressive disorder	Duloxetine, mirtazapine, topiramate	Patient reported taking mirtazapine, 135 mg/day, while the medication overview of the mental health care department stated mirtazapine 45 mg/day	Difference in dose	3	Yes	Re-evaluate total medication use (reconsider the dosages and combinations of psychotropic drugs; evaluate whether patient is taking them as prescribed)
Depressive disorder	Rosuvastatin, metoprolol, omeprazole, acetylic acid, metformin, long-acting insulin, short-acting insulin	Patient was taking metoprolol, 190 mg/day, which was absent from the medication overview of the mental health care institution	Omitted drug	3	Yes	Consider replacing a current drug (replace metoprolol with atenolol or another non-lipophilic $\beta$ -blocking agent, as lipophilic $\beta$ -blocking agents may induce or worsen depressive symptoms)

<sup>a</sup> As assessed during medication reconciliation.

<sup>b</sup> Class 1 = discrepancies unlikely to cause patient discomfort or clinical deterioration, class 2 = discrepancies that could potentially cause moderate discomfort or clinical deterioration, class 3 = discrepancies that could potentially cause severe discomfort or clinical deterioration.  
DSM Diagnostic and Statistical Manual of Mental Disorders; N/A not applicable; SIADH syndrome of inappropriate antidiuretic hormone (ADH) secretion.

Table 2 shows a few examples of discrepancies and their classification. The clinically relevant discrepancies (class 2 or 3) affected 49.3% of all patients. The percentage of clinically relevant discrepancies did not significantly differ between outpatient departments ( $p=0.440$ ) or between academic and community settings ( $p=0.379$ ).

In comparison, 80.5%, 15.6%, and 4.2% of the medication discrepancies from general practitioners and 86.9%, 9.9%, and 3.2% of those from pharmacies were categorized as class 1, 2, and 3 discrepancies, respectively. Class 2 and 3 discrepancies from general practitioners and pharmacies were present in 33.2% and 22.3% of patients, respectively.

In 35.4% of all patients, the expert panel considered intervention clinically necessary as a result of a discrepancy at the outpatient department. Initial agreement for judging the intervention necessity was limited (Cohen  $\kappa=0.13$ ; 95%CI 0.06–0.20), but this was solved by consensus in all cases. The expert panel suggested a mean $\pm$ SD of 0.5 $\pm$ 0.7 interventions per patient, with “consider measuring a somatic parameter” (38.4%) and “re-evaluate total medication use” (37.8%) most frequently suggested.

## DISCUSSION

This study indicates that medication reconciliation processes at outpatient departments for mood and anxiety disorders are potentially harmful and in need of improvement. Patients had a mean of 3.9 discrepancies. Moreover, almost 23% of all discrepancies had the potential to cause moderate to severe discomfort or clinical deterioration, affecting almost half of all patients. These figures were lower for general practitioners and community pharmacies.

To the best of our knowledge, this is the first study worldwide to evaluate whether mental health care providers are aware of the drugs used by their outpatients when they visit them. Previous studies<sup>4,10-14</sup> in non-psychiatric outpatient departments, such as those for haemodialysis or internal medicine, found on average 0.97 to 3.4 discrepancies per patient. A single study<sup>6</sup> investigating psychiatric inpatients after admission to a geriatric psychiatric clinic showed discrepancies in 78% of 50 patients, with a median of 2 discrepancies per patient. While these results are in line with the numbers reported for general hospital inpatients<sup>5</sup>, we found fairly higher discrepancy frequencies in psychiatric outpatients, which indicates that this issue may especially be unknown and problematic in psychiatric outpatient settings. In addition, we observed no differences in the discrepancy risk or associated patient harm between the participating outpatient departments or between academic and community settings. Moreover, we found high numbers and clinical relevance of discrepancies, despite the generally high quality of health care in the Netherlands and in particular a guideline demanding a complete and up-to-date medication overview with every contact between patient and prescriber. Therefore, although replication is warranted, we believe our results apply to psychiatry outpatient departments in general.

There are several potential explanations for the higher discrepancy frequencies in psychiatric outpatients. First, these patients often have more than one health care provider (e.g., psychiatrist and general medical physician). This makes it difficult to keep track of changes in drug regimens made by different prescribers. Indeed, the number of prescribing physicians has been shown to increase medication discrepancies in outpatients.<sup>15</sup> We could not evaluate whether there was a difference in number of discrepancies in prescriptions from the outpatient department and outside doctors, as we did not assess prescribers. Second, higher discrepancy numbers may reflect the often-reported suboptimal treatment of somatic conditions in psychiatric outpatients compared to non-psychiatric individuals.<sup>16</sup> In addition to receiving a lower quality of medical care, psychiatric patients receive fewer prescriptions for several common drugs for existing medical disorders than individuals without mental illness.<sup>16</sup>

In contrast to previous studies in non-psychiatric outpatients, we also determined a measure of potential patient harm due to discrepancies. Assessing clinical relevance is essential to determine the impact of discrepancies. Almost 23% of all discrepancies had the potential to cause moderate to severe patient harm, which, importantly, affected almost half of all patients. Since there is currently no valid and reliable method to pre-identify patients at risk for discrepancies, attention should not be limited to specific subsets of patients when implementing medication reconciliation.

Our results at general practitioners and pharmacies are in line with several studies<sup>15,17-21</sup> in population-based samples visiting primary care physicians. Since general practitioners and community pharmacists at least in some countries have the role of gatekeepers with the responsibility of having an adequate overview of the medication information about their patients, the numbers of discrepancies are still surprisingly high.

In our opinion, our results demonstrate the need for implementation of a structured medication reconciliation process in clinical practice at psychiatry outpatient departments in order to minimize iatrogenic harm to outpatients. In different hospital settings, implementation of medication reconciliation with patient counselling substantially diminished discrepancies upon both admission and discharge in various countries.<sup>5,22-24</sup> In addition, medication reconciliation upon hospital discharge resulted in higher benefits than costs related to the net time investment.<sup>25</sup> Furthermore, prescribing safely and conducting adequate somatic monitoring of psychiatric patients as recommended by guidelines are impossible without a complete and up-to-date medication overview.<sup>26,27</sup> We therefore developed an innovative care path called Monitoring Outcomes of psychiatric Pharmacotherapy (MOPHAR), which is currently being implemented. In this care path, a nurse conducts medication reconciliation with each patient at every visit to a prescriber. In case of relevant medication discrepancies, MOPHAR will notify the treating psychiatrist. After reconciliation, recommended (somatic) monitoring is performed according to pre-specified protocols per drug used. This information is immediately available in the electronic medical record in summarized form, thus instantly providing mental health care providers with up-to-date information on medication use and monitoring parameters.

We will investigate the impact of this integrated care model regarding the benefits for psychiatric patients.<sup>28,29</sup>

Strengths of this study are the large population and the conduct of assessments at four different locations. However, a few limitations need to be considered. First, our study might suffer from performance bias, as collaboration of outpatient departments may have been selective for well-organized settings. This may have resulted in an underestimation of discrepancies, meaning true practice is more alarming still. Second, medication reconciliation involving psychiatric patients may not be as reliable as in other patient populations. However, medication reconciliation through combination of pharmacy records and patient counselling is currently considered the gold standard for determining the actual medication use. It is important to remark that this patient-reported medication use may not reflect the intended or correct use in a pharmacotherapeutic sense. Third, some medication overviews contain theoretical starting and end dates for medication refills that may not correspond with actual use by patients. However, we assume we covered most unintentional discontinuation periods by the 28-day permissible gap for medication refills. Fourth, we did not distinguish between different sources or reasons for discrepancies, such as clinical misunderstandings, clinical errors, or administrative errors. In clinical practice, it is important to make this distinction to resolve the discrepancy accordingly. Fifth, the classification method used to assess clinical relevance is, strictly speaking, unvalidated. However, this procedure has been used in previous studies on medication discrepancies and errors.<sup>6,8,30</sup> Finally, our measure of clinical relevance concerned potential harm. Because of the cross-sectional design of this study, we were not able to collect evidence for actual adverse effects as a result of the discrepancies.

In conclusion, this study shows that outpatients with mood and anxiety disorders may be at substantial risk of medication discrepancies that may be clinically relevant in almost half of the patients. We consider this risk a potentially general problem in the treatment of psychiatric outpatients, for which we suggest that medication reconciliation processes be improved to increase medication safety in psychiatric outpatients.

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