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Instructions for clinical and biomarker monitoring in the Summary of Product Characteristics (SmPC) for psychotropic drugs: Overview and applicability in clinical practice

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Abstract

The Summary of Product Characteristics (SmPC) for psychotropic drugs includes instructions for clinical and biomarker monitoring intended to optimise effectiveness and minimise harm. The present study evaluated which monitoring instructions are given in the SmPCs, and assessed whether instructions are informative enough to be applicable in clinical practice. Monitoring instructions were collected from complete SmPCs for psychotropic drugs (n=70). Reasons and requirements for monitoring were assessed and somatic parameters were distinguished from non-somatic parameters. Instructions were evaluated using the Systematic Information for Monitoring (SIM) score and considered applicable when a SIM score of $\geqslant$3 was found. An average of 3.3 (range 0–13) instructions per drug label was found. Monitoring was primarily for safety reasons (78%). Requirement was predominantly mandatory (71%). Somatic parameters were most often mentioned (80%). Only 34% of the instructions were determined applicable. Overall, an average SIM score of 2.0 (SD=1.7) was found (out of a maximum possible score of 6). In conclusion, prescribing of psychotropic drugs is accompanied by diverse instructions aimed at improving safe use. However, most instructions on monitoring do not provide sufficient information to be applicable in clinical practice.

Keywords

Psychiatry, monitoring, psychotropic drugs, drug safety

Introduction

Treatment with psychotropic drugs aims to relieve mental disorders effectively with no or acceptable adverse effects in terms of tolerability or harm. For each individual patient, the balance between benefit and harm should be assessed before initiation, as well as being continuously evaluated during medication use (Mitchell, 2009). A Summary of Product Characteristics (SmPC) is published by the regulatory authorities for every drug and can be regarded as a user manual. The SmPC includes instructions for monitoring intended to optimise safe and effective prescribing by health-care professionals, as well as optimising drug use by the patient (European Commission, 2009; European Medicines Agency, 2001).

The Hospital Admissions Related to Medication (HARM) study showed that 13% of all possibly preventable drug-related hospital admissions in The Netherlands were related to inadequate monitoring (Leendertse et al., 2008). Adequate monitoring requires that the instructions are clear with respect to what to monitor, when to start monitoring, when to stop monitoring, the frequency of monitoring, what the critical value is and how to respond (Floor-Schreudering et al., 2014).

Psychotropic agents often exert a broad pharmacological effect on neurotransmitter systems (Blier and El Mansari, 2013). For this reason, psychotropic drugs can induce a diversity of psychiatric and somatic side effects. In addition, there often is a substantial lag time (e.g. in treatment with an antidepressant) between starting the drug and a therapeutic response, whereas side effects may present more quickly after treatment initiation (Gelenberg and Chesen, 2000). Gurwitz et al. (2000) showed that psychotropic drugs (together with anticoagulants) were the most common medications with preventable adverse effects in nursing homes. Preventable errors occurred predominantly in ordering (68%) and monitoring (70%) stages. Most observed monitoring errors consisted of inadequate laboratory monitoring or of a delayed response – or failure to respond – to signs or symptoms of drug toxicity or laboratory evidence of toxicity. Therefore, it is expected that monitoring is especially important for psychotropic agents.

Monitoring can consist of both clinical and biomarker monitoring. Clinical monitoring includes the observation of symptoms or signs without the use of a medical test (e.g. checking for

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symptoms of tardive dyskinesia). Biomarker monitoring is divided into two categories: the measurement of physical parameters (e.g. heart rate and rhythm, blood pressure) or of laboratory parameters (e.g. drug plasma concentrations or potassium levels). Monitoring can be primarily aimed at efficacy evaluation or used for the (early) detection of side effects.

More than half of physicians indicated that they use the SmPCs as a source of information (Vromans et al., 2013). Prior research of laboratory monitoring instructions in the SmPCs found an average of 2.8 instructions for laboratory monitoring per drug for the 200 most frequently prescribed drugs in The Netherlands. Only 17% of these instructions contained sufficient information to be applicable in clinical practice (Geerts et al., 2012). A review of the French SmPCs by Rougemont et al. (2010) found a deficit in information concerning relevant therapeutic drug-monitoring information in the SmPCs for psychotropic drugs. It is not known if the information concerning all monitoring instructions is sufficiently described within the SmPCs for psychotropic drugs.

The aim of this study was to identify which monitoring instructions are given in the SmPCs for psychotropic agents in order to determine the reasons for monitoring and to assess whether these instructions are applicable in clinical practice.

Methods

Selection of the SmPCs for psychotropic drugs

All oral formulations of psychotropic agents with a European or Dutch marketing authorisation and available in the Netherlands in April 2014 were included. Psychotropic agents were defined as antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, psychostimulants and mood stabilisers (Appendix 1). The SmPCs were obtained from the website of the Dutch Medicines Evaluation Board (MEB) or the European Medicines Agency (EMA) by searching for the generic name. For every psychotropic drug, the most recently updated version of the registered SmPCs was assessed.

Selection and classification of instructions for monitoring

All monitoring instructions were collected by examining the complete SmPCs that were included. An instruction for monitoring was defined as a statement in the SmPCs to do something prior to or during use of a drug. This included both measurements of (possible) side effects and measurements of co-morbidities. Monitoring instructions for efficacy reasons only were excluded in this analysis, since efficacy should always be evaluated for psychotropic drugs. Instructions for monitoring parameters mentioned in multiple sections of the SmPCs were combined. Monitoring instructions for a combination of drugs, possible intoxications or drugs directed specifically at either neonates or pregnant women were excluded. Confirmation of contraindications or abnormal physiology was not regarded as monitoring. Liver failure as a contraindication, for example, was not regarded as an instruction, but monitoring of liver function for patients with known liver failure was included.

All monitoring instructions were classified in five ways. First, it was determined whether the instructions concerned clinical or biomarker monitoring of physical or laboratory parameters. Clinical monitoring was defined as monitoring of observational signs or symptoms (e.g. tardive dyskinesia, seizures). Biomarker monitoring was defined as the measurement of either physical parameters (e.g. ophthalmological examination, weight, blood pressure, heart rhythm) or laboratory parameters (e.g. potassium, sodium, genotyping, creatinine).

Second, a distinction between monitoring of somatic and non-somatic parameters was made.

Third, the reasons for monitoring were classified as drug selection, dose adjustment, safety, a combination of reasons or not specified. A combination of these reasons was possible for each instruction.

Fourth, based on the wording of the instructions (e.g. 'must' was mandatory, 'advised' was recommended and 'can be' was determined as can be considered), the monitoring requirement was categorised into either mandatory or recommended. If instructions fell outside these categories, the monitoring requirement was counted as 'other' (e.g. mandatory after presentation of defined symptoms, recommended after presentation of defined symptoms, can be considered or can be considered after presentation of defined symptoms).

Finally, the applicability of the instructions was determined. Since there is no gold standard for the assessments of monitoring instructions, we used the Systematic Information for Monitoring (SIM) score, as shown in Table 1. This scale has been used in previous studies for the assessment of the quality of monitoring instructions (Ferner et al., 2005). The following information was collected from the SmPCs to assess the applicability: 'what to monitor', 'when to start monitoring', 'when to stop monitoring', 'how frequently to monitor', 'critical value/what to look for' and 'how to respond'. 'What to monitor' had to be sufficiently specific (e.g. 'monitor potassium and sodium' instead of 'monitor electrolytes'). Each item was given a score of 1 (information is clearly described) or 0 (information is not clearly described).

For each monitoring instruction, the total SIM score was calculated, with possible values ranging from 0 to 6. A monitoring instruction was classed as applicable in cases of a SIM score of $\geqslant 3$. Depending on the characteristics of the instruction (reason for monitoring, clinical/biomarker monitoring, somatic/non-somatic), different items can be seen as essential. Therefore, we decided to weigh each item equally for the applicability.

The first author (MN) reviewed all SmPCs and collected data on instructions. The other three authors (AE, LS and EH) each independently reviewed a random selection of 10% of the SmPCs. All authors agreed in >95% of the random sample. Discrepancies between the reviewers were discussed and resolved by consensus.

Data analysis

To demonstrate what should be monitored for different types of psychotropic agents, all instructions for monitoring in the SmPCs were assessed. Monitoring subjects (e.g. monitoring of kidney function) of instructions within a subgroup (e.g. antipsychotics, antidepressants) were assessed to analyse the main topics of monitoring. To provide an overview, only the most quantitatively described instructions (>20% of the SmPCs per subgroup) were

Table 1. Systematic Information for Monitoring score (Ferner et al., 2005).

Items of information	Necessary content for score=1	Example scoring	Score
What to monitor	Test is sufficiently specific	Cardiovascular examination	0
		Heart rate	1
When to start monitoring	Moment to start monitoring is specified	It is recommended to monitor potassium periodically	0
		Monitor potassium before start of treatment	1
When to stop monitoring	Moment when to stop monitoring is specified, e.g.: 1. When in reference range 2. After stopping treatment 3. After explicit period	Monitor potassium in the beginning of treatment	0
		Monitor potassium two days after initiation	1
How frequently to monitor	Frequency of monitoring is specified	Periodically	0
		Every three months	1
Critical value	Critical value is specified	Renal function	0
		Renal function (MDRD <10)	1
How to respond	Therapy adjustment is specified	Monitoring of tardive dyskinesia is advised	0
		If signs or symptoms of tardive dyskinesia appear in a patient, a dose reduction or discontinuation should be considered	1

Table 2. Characteristics of instructions for monitoring.

Characteristics	Number of medicine	Average number of instructions (range)	Instructions composed of			Monitoring of somatic parameters (%)	Monitoring of non-somatic parameters (%)
			Clinical monitoring (%)	Biomarker monitoring			
				Physical parameters (%)	Laboratory parameters (%)		
All psychotropic drugs	70	3.3 (0–13)	36	38	26	80	20
Antipsychotics	19	4.5 (1–13)	26	48	26	98	2
Anxiolytics, hypnotics and sedatives	23	0.3 (0–3)	17	17	67	83	17
Antidepressants	21	4.1 (1–9)	44	33	23	30	70
Psychostimulants	3	8.7 (6–13)	58	42	0	50	50
Mood stabilisers	4	7.3 (5–11)	28	24	48	86	14

presented in the results section. Since the subgroup of psychostimulants (only three drugs) and the mood stabilisers (four drugs) were small, only the instructions described in more than half of the SmPCs were presented. When more than half of the collected instructions were directed to a specific patient group (e.g. diabetics), this was added as additional information.

Results

Seventy SmPCs for oral psychotropic drugs were included. At least one monitoring instruction was found in 50 (71%) SmPCs. Overall, an average of 3.3 (range 0–13) instructions for clinical and biomarker monitoring were identified. The SmPCs for psychostimulants contain the most instructions for monitoring (8.7) per drug, followed by mood stabilisers (7.3), antipsychotics (4.5) and antidepressants (4.1; see Table 2). Anxiolytics, hypnotics and sedatives (0.3) contain the least instructions for monitoring, with only six monitoring instructions in 23 SmPCS.

Of all psychotropic drugs, 36% of the instructions concerned clinical monitoring, 38% concerned physical parameters and 26% were instructions for laboratory parameters. In the individual drug classes, the monitoring instructions were relatively equally divided between clinical, physical and laboratory monitoring, except for psychostimulants. For psychostimulants, 58% of the instructions concerned clinical monitoring, 42% physical monitoring and no laboratory monitoring.

Somatic parameters were the main subject of monitoring (80%) with variation between drug categories: instructions for antipsychotics, anxiolytics, hypnotics and sedatives, and mood stabilisers existed mostly of somatic monitoring. The high number of instructions for psychostimulants was equally divided into somatic and non-somatic monitoring. In contrast to other psychotropic drugs, the majority of instructions for monitoring of antidepressants aimed to control non-somatic symptoms. It is noteworthy that all instructions that consisted of non-somatic monitoring comprised clinical monitoring.

Table 3. Reasons and requirements for monitoring for all instructions (*N*=232) and per drug category.

Monitoring instructions	Reason for monitoring (%)				Monitoring requirement (%)		
	Drug selection	Safety	Dose adjustment	Not specified	Mandatory	Recommended	Other
All psychotropic drugs (*N*=232)	9	78	5	19	71	19	10
Antipsychotics (*n*=85)	13	85	7	9	60	35	5
Anxiolytics, hypnotics and sedatives (*n*=6)	17	67	33	33	100	–	–
Antidepressants (*n*=86)	6	81	1	19	71	13	16
Psychostimulants (*n*=26)	4	69	0	31	92	4	4
Mood stabilisers (*n*=29)	10	55	10	34	79	3	17

As shown in Table 3, the main reason for monitoring for all psychotropic drugs was to monitor for safety (78%). Other reasons for monitoring were drug selection (9%) and dose adjustment (5%). For the remaining 19% of the instructions, the reason for monitoring was not specified. Dose adjustment was a secondary reason for anxiolytics, hypnotics and sedatives, while for all other subgroups drug selection was the secondary reason. In 9–34% of the instructions within drug categories, a reason for monitoring was not described.

Differences in monitoring requirements could be distinguished between the monitoring instructions. Monitoring was mandatory for 71% of the instructions and was recommended for 19%, with only a few instructions (10%) stating that monitoring was recommended or mandatory after presentation of clinical symptoms (Table 3). All instructions for anxiolytics were mandatory. Antipsychotics had a relatively high number of instructions for monitoring that were recommended (35%), followed by antidepressants (13%), psychostimulants (4%) and mood stabilisers (3%). Other monitoring requirements (e.g. after clinical presentation of signs or symptoms) were found in instructions for mood stabilisers (17%), antidepressants (16%), antipsychotics (5%) and psychostimulants (4%).

An overview of the monitoring instructions is shown in Table 4. No monitoring instructions are mentioned for anxiolytics, hypnotics and sedatives, since none of the instructions was represented in at least 20% of the SmPCs. Some of the instructions are directed to specific patient populations.

Antipsychotics required monitoring of the QT interval (the time from the start of the Q wave and the end of the T wave in the heart's electrical cycle), weight and symptoms or signs of hyperglycaemia. For diabetics or patients with risk factors for diabetes, it was also necessary to monitor blood glucose. Thereby, it is advised to monitor electrolytes and development of tardive dyskinesia. Monitoring of blood pressure was often advised, but it was mandatory for the elderly. Ophthalmic examination was advised for patients using phenothiazines (e.g. perphenazine), but it was also recommended in SmPCs for some other antipsychotics (e.g. flupentixol).

Clinical monitoring of suicidal behaviour, convulsions and blood pressure is mandatory for antidepressants. Haematological examination is advised after presentation of symptoms of sore throat, fever or other signs of infection. Control of the QT interval was mandatory for patients with a cardiac disease or after presentation of signs of heart arrhythmias.

For psychostimulants, monitoring of aggressive or hostile behaviour, blood pressure, cardiovascular status, heart rate, neurological signs and symptoms, suicidal behaviour and symptoms of anxiety and tics is mandatory.

The SmPCs for mood stabilisers describe monitoring of suicidal behaviour, haematological examination, hepatic function and thyroid function as mandatory. Thereby, monitoring of drug plasma concentration and renal function was mentioned.

Table 5 shows the applicability of the total number of instructions, and the instructions represented >10% of all SmPCs for psychotropic drugs. An average SIM score of 2.0 (*SD*=1.7) was found for all instructions for clinical and biomarker monitoring. Two-thirds of the instructions were not applicable in clinical practice (66%) based on the SIM score. Information on a critical value (84%) or when to stop monitoring (74%) was often missing in the instructions. The information mentioned most was when to start monitoring (51%), followed by what to monitor (37%) and how frequently to monitor (34%). Of the most mentioned instructions, monitoring of the QT interval provided most information with an average SIM score of 3.5. However, all instructions for convulsions were considered applicable.

Monitoring of suicidal thoughts and symptoms was most often mentioned throughout the SmPCs. These instructions included that monitoring should be started at the start of treatment (when to start, 85%) and after dose adjustments (how frequently, 85%). In more than half of the instructions, information was missing on when to stop monitoring, when to respond (a critical value was missing) and how to respond and specific symptoms for monitoring. Therefore, a low average SIM score of 1.8 was found.

In multiple SmPCs, it was mentioned that 'appropriate monitoring' was mandatory for specific patient populations, for example for patients with a heart condition or with increased intraocular pressure. However, what to monitor was not clear in these instructions. Consequently, a low average SIM score of 0.4 was found.

For 21% of the psychotropic drugs, assessment of an electrocardiogram was required prior to or after administration to prevent the risk of QT interval elongation. Most of the instructions for monitoring related to the QT interval or convulsions were applicable. All instructions for convulsions were applicable, with an average SIM score of 3.0.

Discussion

A mean number of 3.3 instructions for monitoring were found in the SmPCs for psychotropic drugs. Although psychotropic drugs

Table 4. Instructions for monitoring of psychotropic drugs found in >20% of the SmPCs per drug category (>2 instructions for psychostimulants and mood stabilisers), what to monitor and for what population.

Monitoring instructions	Number of monitoring instructions included in SmPCs/total number of SmPCs	Specific population (>50%)
Antipsychotics (n=19)		
Tardive dyskinesia	11/19	–
Blood glucose	10/19	Diabetics (70%), patients with risk factors for diabetes (50%)
Appropriate monitoring	8/19	
QT interval/ECG	8/19	
Weight	6/19	
Symptoms or signs of hyperglycaemia	5/19	
Electrolytes	5/19	
Blood pressure	4/19	Elderly (50%)
Ophthalmic examination	4/19	
Anxiolytics, hypnotics and sedatives (n=23)		
Not specified	0/23	
Antidepressants (n=21)		
Suicidal behaviour	21/21	
Appropriate monitoring	11/21	Patients with increased intraocular pressure (64%)
Haematological examination	10/21	Patients with sore throat (70%), fever (70%) or other signs of infection (80%)
Convulsions	6/21	Patients with controlled epilepsy (100%)
QT interval/ECG	5/21	Patients with cardiac disease (100%) or signs of heart arrhythmias (60%)
Hepatic function	5/21	
Blood pressure	5/21	
Psychostimulants (ADHD medication and modafinil; n=3)		
Aggressive or hostile behaviour	3/3	
Blood pressure	3/3	
Cardiovascular status	2/3	
Heart rate	2/3	
Neurological signs and symptoms	2/3	
Suicidal behaviour	2/3	
Symptoms of anxiety and tics	2/3	
Mood stabilisers (n=4)		
Suicidal behaviour	3/4	
Appropriate monitoring	3/4	
Haematological examination	2/4	
Hepatic function	2/4	
Drug plasma concentration	2/4	
Renal function	2/4	
Thyroid function	2/4	Patients with hypothyroidism (50%)

SmPC, Summary of Product Characteristics.

are registered for psychiatric indication, most monitoring is directed at somatic parameters. However, there are differences between categories. While a low number of instructions are described for anxiolytics, hypnotics and sedatives, the contrary is found for psychostimulants, mood stabilisers, antipsychotics or antidepressants. Antidepressants are the only group of psychotropics where the majority of monitoring instructions consisted of non-somatic symptoms. Most instructions provided in the SmPCs are mandatory. Two-thirds of the instructions are not applicable in clinical practice.

A major issue concerning the instructions is the low amount of information provided, leading to ambiguous instructions. Recently, Warnier et al. (2014) concluded that a clear message on QT prolongation was lacking in the SmPCs. Of all instructions, we found a relatively high SIM score for monitoring of QT prolongation, but necessary information was still missing. The description of other instructions is worse. An example of the ambiguous monitoring is the instruction for 'appropriate monitoring' which was for example directed to patients with a heart condition. In none of the instructions was it mentioned what to

Table 5. Applicability of the most frequent instructions (>10%) in the SmPCs of psychotropic drugs (*n*=70).

Monitoring instruction	Percentage of SmPCs (%)	What to monitor (%)	When to start monitoring (%)	When to stop monitoring (%)	How frequently to monitor (%)	Critical value (%)	How to respond (%)	Average SIM score (±*SD*)	SIM score ⩾3 (%)
All instructions (*N*=232)	–	37	51	26	34	16	32	2.0 (±1.7)	34
Control for suicidal thoughts and symptoms	37	0	85	0	85	0	12	1.8 (±0.6)	4
Appropriate monitoring	28	0	10	5	5	0	20	0.4 (±0.9)	5
QT interval/electrocardiogram	21	80	87	53	53	27	47	3.5 (±1.5)	73
Haematological examination	20	14	86	86	71	0	14	2.7 (±1.2)	86
Blood pressure	15	100	45	27	18	0	9	1.9 (±1.2)	27
Tardive dyskinesia	15	0	91	0	0	0	45	1.4 (±0.5)	0
Blood glucose	15	36	27	27	18	73	18	2.0 (±1.9)	27
Hepatic function	14	10	40	30	10	10	50	1.6 (±1.9)	30
Weight	11	100	25	25	25	0	25	2.0 (±1.6)	25
Electrolytes (not specified) or potassium, magnesium and sodium	11	38	50	38	38	0	50	2.1 (±2.2)	38
Convulsions	10	100	0	0	0	100	100	3.0 (±0.0)	100

monitor. Another example is the recommendation of electrolytes, sometimes mentioned as 'periodic electrolyte monitoring is recommended', without additional information to clarify this instruction. Clear guidance for monitoring of psychotropic drugs is required and should be provided in the SmPCs by the registration authorities, since most instructions are not applicable. If the physician is expected to live up to these instructions, there should be clarity about what to monitor, when to start monitoring, when to stop monitoring, how frequently to monitor, critical values and how to respond. Evidence for monitoring needs, methods and outcomes should ideally be provided to explain the rationale for monitoring. In clinical practice, guidelines are developed for some psychotropic drugs (e.g. lithium, clozapine) with more informative monitoring instructions. These guidelines can be complementary to the SmPCs. Professional organisations and regulatory authorities together should try to bridge this gap.

On the one hand, it could be debated whether it is clinically relevant to monitor all items stated in the SmPCs. On the other hand, additional monitoring should possibly be recommended based on recent or known insights. For most psychotropic drugs, monitoring was determined as mandatory, leading to additional costs of treatment. To prevent unnecessary costs of monitoring or costs by harm to patients, more research is needed to determine the clinical relevance for monitoring and to provide applicable instructions.

The ambiguity of the instructions may be due to a concern for liability of the drug company/registration authorities and prescribers (Nutt, 2006). A drug company may be liable if a side effect of unexpected reaction occurs outside the monitoring parameter 'window'. Conversely, if too specific, the prescriber could in theory be held liable if he/she did not follow every single monitoring parameter. Additionally, it should be noted that it is not an easy task to create clear and informative instructions where evidence is poor on coping with risk, such as in the situation of QT prolongation.

Some instructions in different SmPCs seemed to be duplicated, for example the warning to monitor suicidal behaviour. The information on suicidal behaviour in the SmPCs for antidepressants is identical for the different antidepressants. These instructions may have been added in these SmPCs by the registration authorities in response to a safety warning by FDA's MedWatch (U.S. Food and Drug Administration, 2014).

This study has some strengths and limitations. A strength of this study is that it was a descriptive study that specifically examined monitoring instructions of SmPCs for psychotropic drugs. We also added whether the instructions were directed to specific patient populations. This information reveals that not all monitoring advice is necessary for patients without co-morbidities. Furthermore, the requirement for monitoring was analysed, providing information on the need for monitoring. Insight into the nature of monitoring is provided by dividing the instructions between somatic or non-somatic monitoring.

In this article, we investigated instructions present in the SmPCs for oral psychotropic drugs. The SmPCs for parenteral formulations were additionally evaluated, but the data are not shown, since there were only minor differences. We do not know whether the applicability of instructions is similar in other European countries, as, apart from a national procedure, medicine can be registered by a centralised, decentralised or mutual recognition procedure in Europe. We have no reason to believe the instructions in Dutch SmPCs differ greatly from those in other countries, but more research is needed to confirm this.

Differences in SIM scores can be observed compared with Geerts et al. (2012). We did not interpret the advice to monitor 'periodically' or 'frequently' as applicable. The frequency should be specified for this item to be applicable. 'Periodically' could imply daily, weekly, monthly or even yearly. Thereby, Geerts et al. (2012) considered instructions for laboratory monitoring applicable when at least three essential items scored one point (the essential items being 'what to monitor', 'critical value' and 'how to respond'). In contrast, we emphasised that a critical value, for example, is not always more important than other items for the applicability. Critical values can often be found in guidelines and can vary among patients. The moment of initiation of

monitoring can also be essential to prevent harm in psychiatric patients, for example by controlling the QT interval prior to prescribing a drug. Even though we weighed all items of the SIM score equally and thereby less strictly, still only 34% of the instructions were considered applicable.

One limitation of this study is the possible subjective evaluation of inclusion of an instruction for monitoring. However, instructions were evaluated independently by multiple authors, and when doubts were present, consensus was reached. Guidelines were not assessed, since most guidelines focused on the indication for the drug, instead of the drug itself. An instruction was deemed applicable when a SIM score of ⩾3.0 was found. Necessary information could still be missing. Although it is also key to monitor the effectiveness of pharmacotherapy, we did not include monitoring instructions on effectiveness in this study.

This study provides a review of monitoring instructions for psychotropic drugs. Additional monitoring can be necessary when combined with other medicines. For a co-morbidity to be confirmed, it can be necessary to monitor specific parameters. As co-morbidities are often known, we did not include monitoring for confirmation of a contraindication as an instruction. Liver function and renal function as a contraindication, not presented as an instruction, were mentioned in 50 and 34 SmPCs, respectively. It could be debated that these should be monitored too.

In conclusion, a mean of 3.3 monitoring instructions was found for psychotropic drugs. Strikingly most monitoring instructions involved somatic parameters. Monitoring is mandatory for 71% of the instructions for clinical and biomarker monitoring. The main reason is for patient safety compared with dose adjustment or drug selection. There is an urgent need for clear instructions to prevent harm. Despite the need for guidance on how to perform clinical and biomarker monitoring, we found that necessary information for clear instructions was missing in the majority of the instructions (66%). For monitoring in clinical practice, it is therefore important that more informative instructions are provided by professional organisations and the regulatory authorities.

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