CHAPTER 15

Multidose Drug Dispensing in Primary Care: A Review of the Literature

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Abstract: Multidose drug dispensing (MDD) is an adherence aid that provides patients with machine-dispensed medicines in disposable unit bags, usually for a 14-day period. The system has been implemented in primary care in some European countries. This review aims to summarize the current evidence on the MDD system's effect on patient safety in home-dwelling patients. We found 60 peer-reviewed articles from five different countries. The studies indicate that MDD has both positive and negative effects on patient safety, and can affect all steps in the medication-use process: prescribing, dispensing, administration and monitoring. Specifically, MDD can increase medication adherence and reduce discrepancies in medication records for patients in primary care. However, it also seems to result in more inappropriate prescribing and more medication errors during discharge from hospitals. In order to improve the MDD system, it is necessary to involve all actors in the medication-use process and define their responsibilities. Specifically, we see that there is a need for better systems to identify patients during care transitions, and increased involvement of the patients themselves.

Keywords: Multidose drug dispensing, primary care, patient safety, review, dose administration aid, home care services

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Multidose drug dispensing (MDD) is a dispensing system in which solid medicines (tablets and capsules) are removed from their original packaging and machine packed in disposable plastic pouches (Figure 1). The pouches are labelled with the patient's name and date of birth, the name and strength of the medicines, and the time the medicines should be taken. MDD is common in hospitals around the world, but is also used in primary care in Australia, Finland, Norway, Denmark, Sweden and the Netherlands (Rechel, 2018).

Figure 1. Multidose Drug Dispensing Pouches Reproduced with permission from Apotek 1 Gruppen AS, Norway

When utilized in primary care, MDD has been promoted as an adherence aid to ensure better medical treatment for patients with medication management problems and polypharmacy. The system was expected to reduce medication costs by reducing medicine waste, saving nurses' working time, improving medication adherence, and reducing medication errors (Association of Finnish Pharmacies, 2003; Price Waterhouse Coopers, 2007; Riksförsäkringsverket, 2001). However, the effects of the MDD system on patient safety in primary care has been mostly experience-based rather than evidence-based (Søndergaard et al., 2005, p. 74)

Systematic reviews on patient safety by Sinnemäki et al. (2013), and on MDD in the Scandinavian countries by Halvorsen and Granas (2012) found only seven and 18 studies, respectively. Both groups of reviews

conclude that the expected benefits of the MDD system have been only partly achieved, and that the system can have negative effects, such as increasing polypharmacy and the use of potentially inappropriate drugs. Despite the limited evidence of the MDD system's effects on patient safety, health authorities continue to encourage MDD in primary care, and its use is increasing (Foundation for Pharmaceutical Statistics, 2015; Norwegian Pharmacy Association, 2010; Rechel, 2018).

The review underlying this chapter aims to describe the pros and cons of the MDD system for home-dwelling patients, and summarize the current evidence in order to provide evidence-based knowledge for optimising the MDD system for these patients.

Methods

A scoping review was conducted to gain knowledge on the use of MDD in primary care (Arksey & O'Malley, 2005). Our aim was to produce a broad overview of the existing peer-reviewed literature addressing MDD and patient safety. We searched the databases Pubmed, Embase, Cochrane and SweMed+, using the keywords "apodos", "automated medication/drug dispensing", "automated dose dispensing", "dosisdispensering", "multidose", "multidose dispensing", "multidose drug dispensing", and "unit-dose dispensing". The literature search was broad, semi-systematic (Snyder, 2016), conducted several times, and did not have a time limit. The first search was conducted in 2016 and the last in August 2021. We also contacted authors from Denmark, Finland and the Netherlands (one from each country) asking for more detailed information about their MDD systems.

Titles and abstracts were screened and all articles that included information about MDD were included. Full-text articles were then retrieved and read by two researchers. We also manually searched the reference lists of the included articles to identify papers missed in the search. We included peer-reviewed articles in English or one of the Scandinavian languages.

The inclusion criteria for this literature review were: all qualitative and quantitative studies conducted in a primary care setting or during care

transitions for home-dwelling patients using MDD. Studies on hospital in-patients and nursing home residents were excluded. We did not assess the quality of the included studies, but we have highlighted the longitudinal studies and articles that compare MDD to ordinary prescribing.

The main focus of this review was to describe the impact of MDD on patient safety for home-dwelling patients. We categorized the articles by combining, integrating, and summarizing the main outcomes of the papers according to the main objectives in the included studies (Perestelo-Pérez, 2013). The following categories emerged: medication safety, prescribing quality, and patient perspectives. We have also summarized how the MDD system is organized in the different countries and highlighted differences that might affect patient safety.

Results

Description of the Studies

We found 60 peer-reviewed articles on the MDD system in primary care from five different countries: 22 studies from Sweden, 21 from Norway, nine from the Netherlands, four from Denmark, and four from Finland. Thirty-three studies related to medication use for home-dwelling patients, six were about medication use during care transitions, and 21 studies were about patients' or health care personnel's experiences in various settings.

Organization and Differences Between the Countries

The MDD system varies between the countries. In Sweden, Finland and Norway most MDD users are home care clients (Bardage et al., 2014; Josendal et al., 2020; Sinnemäki et al., 2014). In the Netherlands, however, the largest group of MDD users are home-dwelling patients who get MDD directly from the community pharmacy (Cheung et al., 2014).

In both Sweden and in Norway the prescribing procedure for MDD differs from that of ordinary prescribing. In Sweden, MDD requires a separate log-in procedure which cannot be performed directly from the medical record (Sjoberg et al., 2012). In Norway, ordinary prescriptions

are electronic, while the MDD system is still mostly paper-based (Josendal et al., 2020). In Finland and the Netherlands, the prescribing procedure is the same for patients with ordinary dispensing and MDD (Mertens, personal communication, 22 September; Sinnemäki, personal communication 30 September).

In Finland, the MDD packaging fee is partly reimbursed for home care patients 75 years and older, who use six or more reimbursable prescription medicines suitable for MDD (Sinnemäki et al., 2013). In addition, a medication review should be performed before patients start MDD (Sinnemäki et al., 2014). In Norway and Sweden, the MDD packaging fee is reimbursed for all patients in home care, regardless of age (Bardage et al., 2014; Helfo, 2018). In the Netherlands and Denmark, the MDD service is also reimbursable for patients without home care services if a prescriber authorizes its use (Mertens et al., 2018a; Reuther et al., 2011).

Medication Safety

Health Care Personnel's Views on Patient Safety

We found 12 studies that reported the experiences of health care personnel regarding prescribing, dispensing and administering medicines. Most health care personnel felt that the MDD system improved patient safety, but there were also concerns about unclear routines and responsibilities.

According to health care personnel the benefits of MDD were: the patients got medicines as prescribed; there were fewer errors; and medication management was improved (Bardage et al., 2014; Herborg et al., 2008; Johnsen et al., 2018; Josendal & Bergmo, 2021; Nilsen & Sagmo, 2012; Wekre et al., 2012; Wekre et al., 2011).

Several studies also indicated that the MDD system resulted in a better overview of patients' medication for GPs and nurses (Bardage et al., 2014; Bell et al., 2015; Bergmo et al., 2019; Frøyland, 2012; Wekre et al., 2012). However, some nurses were concerned that a reduction in manual dispensing would reduce their knowledge about drugs (Nilsen & Sagmo, 2012; Wekre et al., 2011), and some felt that the prescribing procedure was so complicated that it might pose a risk to patient safety (Bardage

et al., 2014). Three studies also pointed out that MDD was less flexible when it came to changes in medications/dosages. (Frøyland, 2012; Herborg et al., 2008; Wekre et al., 2011).

The MDD system has its limitations. A reoccurring topic in many of the studies was an unclear division of responsibilities in the MDD system (Heier et al., 2007a; Herborg et al., 2008; Johnsen et al., 2018; Josendal et al., 2021). Some expressed uncertainty as to who can access and update the medication lists for MDD patients, and thus who should be notified about changes (Heier et al., 2007a; Johnsen et al., 2018; Josendal et al., 2021). GPs have also noted that it can be difficult to take over responsibility for medication started by other doctors, and some think that only the GP should be allowed to make changes (Frøyland, 2012; Wekre et al., 2012). In a survey by Nilsen and Sagmo (2012), nurses and nursing assistants stated that MDD reduced their responsibility for errors in the medication management process.

Discrepancies in Medication Records

In eight studies, discrepancies between medication records in primary care were investigated. Discrepancies are common, but MDD might reduce their occurrence.

We found four Norwegian studies investigating discrepancies between medication records from the GP, the home care service and/or the MDD pharmacy. These showed discrepancies in 51–88% of patients' records (Bakken & Straand, 2003; Heier et al., 2007b; Josendal & Bergmo, 2019; Mamen, 2016). In the interview study from Josendal and Bergmo (2019) the GPs, home care nurses and community pharmacists described how discrepancies could lead to unintended changes in the patients' medication regime, when changing from an MDD system based on paper prescriptions to one based on electronic prescriptions.

Sinnemäki et al. (2014) examined how medication lists were reconciled when patients started MDD in Finland. They found that over half of the medication lists were incomplete at initiation, and that 43% of the patients got treatment-related changes and 96% technical changes in their medication lists during initiation. Tiihonen et al. (2016) compared

the medication list in the electronic medical record and actual drug use among home care clients and found that MDD was not associated with having discrepancies.

A cross-sectional study by Josendal and Bergmo (2018) found that the number of patients with discrepancies was reduced from 60% to 29% when comparing medication lists in the initiation of the electronic MDD system in Norway, to lists 2 years after initiation.

We found only one controlled before/after study on discrepancies. In this study, from Wekre et al. (2010), discrepancies in medication records between the home care service and GP were reduced by 34% after implementation of MDD. After implementation, 31% of the patients' records still had discrepancies.

Transitions Between Care Levels

We found nine studies indicating that MDD patients are at an increased risk of medication errors upon hospital discharge.

A case study by Lysen et al. (2011) described two patients whose use of MDD was not noted in the medication records at admission. This resulted in patients continuing their old medications when transferred back to primary care. Another Danish study also found that 14% of changes in MDD patients' medication treatment during hospital stays were not reported to the GP or MDD pharmacy (Reuther et al., 2011).

In a survey and a focus group study of GPs in primary care units in Sweden, participants noted difficulties with managing MDD patients after discharge (Caleres, Bondesson, et al., 2018; Caleres, Strandberg, et al., 2018). Similarly, nurses and nursing assistants reported that there is a need for improved cooperation to minimize medical errors in the transition from hospital to primary care (Bardage et al., 2014). In a study by Alassaad et al. (2013) it was found that 25% of MDD users had discrepancies in their medication records during hospital discharge, and 3% were considered serious.

Three Swedish studies compared patients with MDD to patients with ordinary prescribing during care transitions and found that MDD patients have between three and 18 times increased risk for errors during

discharge from hospitals (Bergkvist et al., 2009; Caleres et al., 2020; Midlöv et al., 2005), but not on admission (Midlöv et al., 2005).

Prescribing Quality

Inappropriate or suboptimal prescribing was the area that was studied the most in the studies included here. Most of the 21 studies found that prescribing quality for MDD patients is poor, and seems to be worse for patients with MDD compared to patients with ordinary prescribing.

Prescribing Quality in MDD Patients

From the cross-sectional studies, we find that MDD users are prescribed more medicines than patients with ordinary prescribing and are more exposed to chronic polypharmacy (Belfrage et al., 2014; Johnell & Fastbom, 2008; Morin et al., 2018; Wastesson et al., 2019).

Several different quality indicators have been used to measure the degree of potentially inappropriate prescribing (PIMs): the Norwegian General Practice Criteria (NORGEP); quality indicators from the Swedish National Board of Health and Welfare; START/STOPP criteria; and the European Union EU(7)-PIM list. Depending on the indicators, the exposure to PIMs varied from 20% to 97% of patients (Belfrage et al., 2014; Halvorsen et al., 2012; Hammar et al., 2014; Josendal et al., 2020; Lesen et al., 2011; Lönnbro & Wallerstedt, 2017; Söderberg et al., 2013). Three studies found that the majority of problematic prescriptions were considered clinically relevant (Belfrage et al., 2014; Hammar et al., 2015; Lönnbro & Wallerstedt, 2017). A Dutch study examining the effect of a pharmacist-led medication review on drug-related problems (DRPs) in older patients found that MDD patients had, on average, 8.5 DRPs (Kwint et al., 2011). In addition, a study from Milos et al. (2014) found that elderly MDD users were using a high number of drugs, which could increase fall risk and cause/worsen orthostatic symptoms.

In the five studies that compared patients using MDD with patients using ordinary prescribing it was found that PIMs and DRPs were up to eight times more common in MDD patients (Belfrage et al., 2014; Johnell

& Fastbom, 2008; Lea et al., 2019; Lönnbro & Wallerstedt, 2017; Sjoberg et al., 2011). However, one study found that MDD was associated with a lower probability of statin use, and one found that MDD users were less exposed to drug-drug interactions and long-acting benzodiazepines than patients with ordinary prescribing (Johnell & Fastbom, 2008; Sundvall et al., 2019)

Changes in Prescribing Patterns After Enrollment in the MDD System

Some studies have also examined data after the enrollment of patients in the MDD system looking at changes in prescribing patterns.

A Swedish longitudinal study of more than 30,000 patients found that initiation of MDD was associated with an increased number of drugs prescribed per patient, and an increased number of PIMs, but fewer drug changes (Wallerstedt et al., 2013). Sjoberg et al. (2012) looked at hip fracture patients at discharge from the hospital and after 6 months. Of these, 107 patients used MDD and 47 patients used ordinary prescribing. They found that MDD patients had fewer drug changes (dosage adjustments, withdrawn or newly prescribed) compared to patients with ordinary prescribing.

Two Finnish studies have looked at patients as they started using MDD. Bobrova et al. (2019) used the European Union EU(7)-PIM list and found that the proportion of patients exposed to clinically significant PIMs increased 6 months after enrollment (59% vs. 64%). The proportion of patients with clinically significant drug-drug interactions was the same at follow-up. The number of medications increased for 61% of the patients. Sinnemäki et al. (2017) found that drug consumption was reduced for 11 of the 20 most used active substances 1 year after initiation of MDD. There were also more starts and discontinuations in the MDD group compared to the control group.

A Norwegian study from Hindhammer et al. (2012) included 1,060 new MDD users, and found that drugs with a potential for abuse was reduced by 11% after initiation of MDD. They also found a normalization of the retrieval of these drugs (i.e., patients with unusually high retrieved

amounts decreased and unusually low amounts increased). The total amount of drugs increased by approximately 10% 1 year after enrollment. However, this was also the case for the control group without MDD.

Changes in Prescribing, Dispensing and Administering Procedures

Three studies described differences in medication-use processes for MDD patients and patients with ordinary prescribing, and an additional three studies described changes in time use for the two systems.

Cheung et al. (2014) used data from the Dutch Central Medication Incidents Registration system to describe medication incidents related to MDD. Of 3,685 reported incidents from community pharmacies, 227 (6.2%) were related to MDD. Most reported incidents occurred while entering the prescription into the pharmacy information system and during filling the MDD bag (e.g., broken tablets). MDD also introduced four new phases within the medication process not present with ordinary prescribing: processing the MDD module; sending the MDD file to the supplier; filling the MDD bag; and adjustment of the MDD bag.

Mertens et al. (2018b) evaluated the MDD process in community pharmacies. Over a 3-week period, 261 MDD adjustments involving 364 drug changes were documented. Of these, 52% were effectuated immediately, and about half of these were effectuated manually. The pharmacists felt that about one quarter of the adjustments could have been deferred. Immediate adjustments took significantly longer than deferred adjustments.

In Josendal et al. (2021) pharmacists identified problems with 11% of the 4,121 MDD prescriptions dispensed. The most common issues were expired prescriptions (29%), drug shortages (19%), missing prescriber signatures (10%), and unclear/missing medication names or strengths (10%). They also discovered that responsibilities and work practice for community pharmacists differed when dispensing MDD prescriptions compared to ordinary prescriptions: they took on more responsibility to get prescriptions renewed, and they did less patient counselling.

In terms of time use, Heier et al. (2007a) and Wekre et al. (2012) reported that GPs found MDD more time consuming than ordinary prescribing. While Frøyland (2012) found that only one third of GPs found MDD more time consuming, while one third found it less time consuming than ordinary prescribing. In Bardage et al. (2014) about one third of GPs reported that MDD limited their time with patients.

Nurses and nursing assistants reported that MDD was less time consuming than ordinary prescribing (Heier et al., 2007a), and that the system did not limit their time with patients (Bardage et al., 2014). Meanwhile, a study from Josendal and Bergmo (2021) reports that both home care nurses and community pharmacists experienced an increased workload with the electronic prescribing system compared to the paper-based system, due to an increased need for clarifications.

Patient Perspectives

Inclusion of Patients in the MDD System

In a questionnaire conducted among GPs, nurses and nursing assistants in Sweden the majority reported that MDD was suitable for patients with memory deficiencies, patients whose medicines are not changed often, patients with many medications, and patients with poor adherence. Most nurses and assistants also responded that MDD is suitable for patients with difficulties opening medicine packages (Bardage et al., 2014). The Danish study by Reuther et al. (2011) concluded that MDD can be suitable for persons who use several drugs long-term, and whose medication is not changed frequently. The pharmacists interviewed in the study by Koster et al. (2016) suggested that the use of aids such as MDD could be a strategy to improve medication use in patients with limited health literacy.

In two studies it has been suggested that MDD is mostly used for the convenience of healthcare staff (Bardage et al., 2014; Wekre et al., 2011), but in a study by Mertens et al. (2018a) it was found that for most home-dwelling patients MDD was initiated after shared decision making. Mertens et al. (2018a) also found that potential medication management problems (functional, organizational, adherence, and medication

knowledge) were more prevalent among MDD users compared to non-MDD users. MDD users were also older, used more medications, and were more often cognitively impaired and frail.

Adherence and Medication Knowledge

Health care personnel generally seem to think that MDD improves medication adherence (Bardage et al., 2014; Frøyland, 2012). However, some are concerned that MDD may reduce patient involvement (Bardage et al., 2014).

In interviews with patients, Larsen and Haugbølle (2007) and Holbø et al. (2019) found that most patients reported incidents where they were non-compliant: taking out tablets, changing the time of the day they took the tablets, or forgetting to take medicines, whether or not they were the medicines in MDD or those they took from their original package. However, the former study reported that MDD did not seem to change the users' understanding of medications, while the latter concluded that MDD patients lack adequate information and adaptations enabling users to get the full benefit of the system.

Mertens et al. (2019) surveyed 62 patients where most felt that MDD had supported them in their medication use and improved their medication management. In a questionnaire study of 1,645 MDD users, Bardage and Ring (2016) reported that the majority of users felt that MDD made it easier for them to remember to take their medication. It helped them take the correct dosage and they felt secure with it. About half of these patients also stated that MDD allowed them to become more involved in decisions about their treatment. However, 12% said they failed to take their medicines, and 25% called for better information from prescribers about the purpose of treatment and on changes in drugs.

Kwint et al. (2013) compared self-reported medication adherence and knowledge in 127 MDD users and 96 non-MDD users. They found that MDD users had higher adherence than non-MDD users (81% vs. 58%), while knowledge about medicines was lower (40% vs. 79%). However, the MDD users reported more knowledge of their manually dispensed drugs compared to their MDD drugs.

Two Dutch studies have measured the time in therapeutic range for vitamin K antagonists in relation to patients using MDD. Van Rein et al. (2018) found that MDD was associated with better adherence in the first month compared to instructing patients, but they found no difference after 4 months. Mertens et al. (2020) found that MDD patients had an increased time in therapeutic range compared to the control group, and thus improved the quality of anticoagulation. There was no reduction in the number of bleedings or thromboembolic events between the intervention and control group.

Discussion

This review, consisting of 60 articles, indicates that MDD increases medication adherence and reduces discrepancies in medication records for patients in primary care. In addition, the MDD system may make it easier to identify medication-related problems and reduce drug-drug interactions. However, MDD also seems to result in more inappropriate prescribing, more medication errors during discharge from hospitals, and may potentially increase the number of drugs prescribed.

Even though MDD is often referred to as a dispensing system and an adherence aid, this review shows that MDD affects more than just dispensing errors and medication adherence. We argue that MDD can affect all steps in the medication-use process: prescribing, dispensing, administration and monitoring. In order to optimise the MDD system and reduce potential negative effects, it is thus necessary to look at the entire medication-use process and all the actors involved.

Administration and Monitoring of MDD Medicines

It is estimated that 50% of patients with chronic illnesses are non-adherent, resulting in poorer health outcomes and increased medical costs (Brown & Bussell, 2011, p. 304). The three quantitative studies on medication adherence in our review all show that MDD users have a higher adherence than non-MDD users (Kwint et al., 2013; Mertens et al.,

2020; van Rein et al., 2018). However, in the interviews and surveys, most patients still said that they sometimes had been non-adherent (Bardage & Ring, 2016; Holbø et al., 2019; Larsen & Haugbølle, 2007). Non-adherence is, however, not always inappropriate. Adjusting medication dosages might be valid as a form of intelligent non-adherence, such as skipping diuretics before going shopping. Other adjustments might be the result of having too little information about or understanding of their medicines or diseases. These adjustments, especially when based on too little knowledge, might increase the risk of errors, such as taking out the wrong tablet from the MDD pouches.

We did not find any studies investigating administration errors in home-dwelling MDD patients. However, a Dutch nursing home study showed that despite MDD reducing the frequency of errors, they still occurred in one fifth of medication administrations. The most common types of errors were the wrong administration technique, and medicines given at the wrong time (van den Bemt et al., 2009). Similarly, the Danish Patient Ombudsman found 4,000 incidents relating to MDD during a one-year period. Half of these incidents were related to the administration of medicines, most commonly that the medicines were not given to the patients, they were given at the wrong times, or the patients did not take the medicine (Pasientombuddet, 2013). So even if MDD ensures that the patient gets the right medications, errors can still occur when the medicines are administered, or the patient might not take the medicine at all.

Interestingly, Kwint et al. (2013) found that medication knowledge was lower in MDD users than non-MDD users, and that MDD users had more knowledge of their manually dispensed medicines compared to those in the MDD bags. It would thus seem that the MDD system reduces the patient's knowledge about medicines. This is similar to findings from studies on other dosing aids. When filled by a third party, dosing aids might reduce the patient's autonomy and knowledge about medicines, and as such be disempowering (Elliott, 2014).

We also find similar results for the health care personnel who administer MDD to patients. Several had concerns that the MDD system reduced their knowledge of medicines (Nilsen & Sagmo, 2012; Wekre et al., 2011).

After introduction of MDD some health care personnel also felt reduced responsibility for medication administration (Nilsen & Sagmo, 2012). If both the nurses and the patient identify symptoms as potential side effects of medications to a lesser degree, this might result in them contacting their GP to a lesser degree as well, which again might result in more inappropriate prescribing for these patients.

Recommendations

- To ensure that the MDD system does not disempower patients, patient involvement in the initiation phase is necessary. There should be clear guidelines as to which target groups should be offered MDD. Included patients should be instructed to report to health care personnel if they experience side effects or other problems with their medications.
- To avoid increased costs for patients and errors when patients adjust their medications, there must be good routines for communicating which medicines should be dispensed as MDD, and which should be dispensed in their original packaging.
- To be able to observe and report effects of the patient's medications, home care nurses need to keep updated on medicines and their side effects.

Dispensing MDD

Some of the rationale behind implementing MDD has been to reduce dispensing errors. We did not find any studies on the accuracy of MDD dispensing in home-dwelling patients, but studies from other settings have shown that dispensing error rates are very low with MDD, and lower compared to manually filled dosing aids (Gerber et al., 2008; Klein et al., 1994; Palttala et al., 2013; Søndergaard et al., 2005).

Even though MDD seems to increase the chance of giving the right medication at the right time, errors can still occur at a later stage. When a physician changes a patient's medication, this may wait until the next MDD delivery, the medicine may be administered on the side until the

next delivery, or the bags may be manually adjusted. Both of the latter options increase the risk of errors, but for certain medications it might be too long to wait until the next delivery. Manual adjustments are also time consuming (Mertens et al., 2018b).

One of the benefits of the MDD system is that it gives the pharmacist a better overview of medication use, including prescriptions from both GPs and hospital physicians. Increased access to medication history also seems to result in pharmacists detecting more errors and inappropriate prescribing of these prescriptions (Josendal et al., 2021). This increased overview has also been suggested as an explanation as to why these patients seem to have fewer serious drug-drug interactions in their medication lists, and use fewer psychotropic medicines (Johnell & Fastbom, 2008).

However, because the MDD system works as a subscription, and many patients get medicines via their home care service, there is limited contact between the patient and the pharmacist during the dispensing process. It would seem that pharmacists do little patient counselling of home care patients with MDD (Josendal et al., 2021). MDD patients have also reported that they would like more information about the medicines they are taking, the reason for use, information about changes in their treatment, and pictures of the tablets that are dispensed in MDD (Bardage & Ring, 2016). Less contact with the pharmacist might be a contributing factor as to why MDD patients have less knowledge about their medicines.

Recommendations

- To avoid dispensing errors, medication changes in MDD should be deferred until the next delivery whenever possible. There should also be a clear agreement with the GP on how to assess whether a change can be deferred.
- To assure that patients get essential information about their medicines, the pharmacist has to provide adequate information about medicine use, either directly to patients or via the home care service. For home care patients, the responsibility for patient counselling should be clearly placed between the pharmacist and the home care service.

- To reduce errors in manual adjustments to MDD bags, the pharmacist needs to supply information on how to identify the MDD tablets.
- To improve quality in prescribing, the pharmacist should use all available information about the patient's medication history in order to assess the medication regime for MDD patients as a whole.

Prescribing for MDD Patients

Several of the included studies reveal that MDD changes doctors' prescribing procedures and prescribing patterns. The majority of studies on this topic are, however, from Norway and Sweden, where there are different procedures for prescribing MDD than for ordinary prescriptions. This in itself can increase the risk of errors. GPs might have to document medication changes in several systems, which might increase the risk of duplicate prescriptions and perhaps result in prescriptions not being sent to the correct system, so the patient never gets the intended changes to their MDD.

However, studies from both Finland and the Netherlands, where the prescribing procedures are the same for MDD patients and patients with ordinary prescribing, also find that MDD patients are frequently exposed to PIMs, DDIs and DRPs (Bobrova et al., 2019; Kwint et al., 2011). Though PIMs are common for elderly patients in general (Nyborg et al., 2012), it seems that they are more common in MDD patients than for patients with ordinary prescribing (Johnell & Fastbom, 2008; Sjoberg et al., 2011). It is, however, difficult to assess whether this is due to the MDD system, or whether this is because the patients with the most complex medication regimes use MDD (see also methodological considerations).

The included articles present possible explanations for why MDD patients have more inappropriate prescribing than patients with ordinary prescribing. One explanation might be that the procedures for renewing prescriptions are too automated and the lists might be reviewed less frequently (Sjoberg et al., 2011; Sjoberg et al., 2012; Wallerstedt et al., 2013). This is supported by two Swedish studies showing that MDD patients have fewer changes in their mediation regimen than patients with ordinary

prescribing (Sjoberg et al., 2012; Wallerstedt et al., 2013). However, the Finnish study from Sinnemäki et al. (2017) found an increased number of starts and discontinuations in the MDD group compared to patients with ordinary prescribing, which might indicate that this is specific to the Swedish prescribing system.

Regardless of whether MDD is the direct reason for poor prescribing quality, we can see that PIMs and DDIs are very common in MDD patients, and action should be taken to improve the prescribing quality for these patients. A possible way to improve quality would be to do medication reviews. Kwint et al. (2011) found that medication reviews can increase the quality of pharmacotherapy for MDD patients, and other studies have also suggested that MDD medication lists can be used to identify patients with PIMs, who can then be selected for medication reviews (Halvorsen & Granas, 2012; Josendal et al., 2020). However, none of the included articles described regular medication reviews as current practice for these patients.

Even though discrepancies between medication lists in primary care are reduced with MDD, the included studies indicate that discrepancies may increase for patients transitioning from secondary to primary care. Errors during care transitions and discrepancies in the medication lists between the hospital and the GP are very common (Foss et al., 2004; Michaelsen et al., 2015; Redmond et al., 2018; Tam et al., 2005); however, the use of MDD increased the risk of these errors occurring (Bergkvist et al., 2009; Caleres et al., 2020; Midlöv et al., 2005). The included articles found that there was an unclear division of responsibility regarding MDD patients at discharge, which might have led to the errors. In particular, it was unclear who had access to and was allowed to change the medications of MDD patients. Unclear responsibility might also explain why an increased number of prescribers increased the risk of inappropriate prescribing (Söderberg et al., 2013).

Recommendations

- To reduce errors and discrepancies in medication lists, there should be uniform procedures for ordinary prescribing and MDD prescribing.

Existing systems should be integrated to reduce the need for double documentation and parallel prescribing procedures.

- To improve quality in prescribing, GPs, in collaboration with other health care personnel, should regularly review the medication lists of MDD patients.
- To avoid errors during care transitions there is a need for clear routines to identify patients with MDD on hospital admission. MDD should be paused during the hospital stay, and the medication list updated after hospital discharge. The hospital's and the GP's responsibility for prescribing and updating the medication list must be clearly defined.

Methodological Considerations

The main purpose of this review was to describe and summarize peer-reviewed studies on safety in MDD patients. We found that the procedures for prescribing MDD, the patients offered MDD, and routines among health professionals handling MDD differed between countries. Furthermore, the studies had different approaches, settings and designs. It is therefore difficult to draw definite conclusions about MDD and patient safety. However, this work gives an overview of the literature and highlights some trends that can be used to improve safety for MDD users.

When interpreting the results, it is important to look at the study designs used. Most of the studies did not have a control group. Even for those with a control group, it was difficult to conclude whether the differences we see in prescribing between the two groups are due to the MDD system or other factors related to the patients offered MDD. Patients using MDD generally use more medicines, have more complex drug regimens, and have trouble managing their own medication. Thus they might not be comparable to patients who do not use MDD. The same is true for the longitudinal studies. We can see that the number of PIMs and total number of drugs increase after initiation. However, we cannot conclude whether this is due to the MDD system, or if there was an increase in medications or medication complexity that resulted in the patients starting MDD.

We also acknowledge that the term "multidose" is not easily defined. Some studies may have used other terms and definitions to describe the prepacking of medicine in pouches.

Conclusions

To summarize, the MDD system has both positive and negative effects on patient safety. MDD has the potential to improve some aspects of medication use, in particular by increasing adherence and decreasing the number of discrepancies between home care services and GPs. However, the MDD system does not solve the problems of potentially inappropriate prescribing, medication errors, and the risk of adverse drug events. On the contrary, the MDD system might increase the risk of such events.

In many of the included studies, unclear routines and division of responsibility were suggested as the causes of the negative effects of MDD. This is not surprising as the MDD system has been implemented with the idea that it would primarily relieve the burden of dispensing tablets from many containers, and ease the administration process of handing over the medicines to the patients. However, as this review shows, the MDD system can affect all phases in the medicine-use process. In order to improve the MDD system, it is thus necessary to involve all actors in the process and define their responsibilities. Specifically, we see that there is a need for better systems to identify patients during care transitions, and a need for increased involvement of the patients themselves.

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