

**Indications for Multi compartment Compliance
Aids (MCA) - also known as Monitored Dosage
Systems (MDS) - provision**

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EXECUTIVE SUMMARY

Non – adherence with medication has considerable health, economic and social implications. Several factors have been implicated in non – adherence, hence the difficulty in addressing the issue. Research identified issues include:

- Difficulty accessing medication from packaging due to manipulation problems
- Sight impairment
 - Difficulty reading the labelled directions, warnings / distinguishing the different medicines
 - Difficulty accessing medication from packaging
- Confusion / forgetfulness
- Complexity of treatment regimen
- Intentional non – adherence

Suggested remedies include:

- Supplying medicines in packaging with appropriate closures
 - bottles with winged caps
- Ensuring directions and warnings can be read and medicines identified
 - Larger font / coloured / coded labels
- Providing memory aids for the cognitively impaired
 - Reminder chart
 - Cues
- Simplifying treatment regimens
 - Medication review
- Multi compartment compliance aids

Provision of a filled Multi compartment Compliance Aid (MCA) - also commonly referred to as Monitored Dosage System (MDS) - can potentially address the issues of difficulty accessing medication and following the regimen due to sight impairment and / or confusion / forgetfulness. The research evidence to support these proposed benefits is however limited.

MCA's are not an appropriate intervention for addressing intentional non-adherence and have been associated with a negative impact on patient autonomy and adherence. Labelling requirements and stability issues limit the type of medicines that can be included in MCA's, creating a potential for greater confusion. Several MCA's are available with varying characteristics, however, little research evidence is in existence to inform the choice of MCA.

Accepting that MCA's may be beneficial to certain patients but have a negative impact on others, it is essential that pharmacists are able to appropriately identify patients for MCA provision. Research has shown that currently used assessment techniques may be inadequate for accurately identifying patients requiring a MCA. Further research is therefore required in order to design a comprehensive patient assessment tool for use by community pharmacists. Further to determination of whether or not a MCA is indicated, the characteristics of the most appropriate device requires identification.

1. Introduction

It is estimated that 50% of all prescribed medication is not used by patients as intended by the prescriber,¹ this behaviour is believed to make a significant contribution to health service costs. The frequency of drug related hospital admissions is reported to range from 2.9% to 5%²⁻⁴ and research has shown that between 11% and 30% of such hospital admissions are due to patients not using their medication as intended by the prescriber.^{5,6}

Non-adherence with a treatment regimen describes any medication taking behaviour unintended by the prescriber or not in accordance with the agreement between the patient and prescriber. This therefore relates to both dose omission and addition by a patient, relative to that prescribed. It also encompasses incorrect method of administration or observance of incorrect dosage intervals.

Non-adherence can be notionally subdivided into unintentional and intentional. Whilst intentional non-adherence is associated with patient beliefs, several factors have been implicated in unintentional non-adherence; drug administration difficulties, sight impairment, confusion / forgetfulness and treatment related issues.

2. Unintentional non-adherence

2.1. Drug administration difficulties

The population with compromised manual dexterity due to neurological and / or inflammatory conditions will often by definition, be in receipt of prescribed medication.^{7,8} If adherence issues are suspected in these patients, possible solutions must therefore be compatible with compromised manual dexterity.

Researchers regularly report the difficulties experienced by patients when using the many different exotic formulations in which medicines are presented. The most commonly used formulation is the solid oral dose as tablets and capsules, generally presented in bottles with child resistant caps or blister packs. These relatively simple packaging and closure devices are known to create difficulties for certain members of the public.

Patient demonstrated ability to access medication from packaging was assessed by a pre-hospital discharge study involving self medicating patients aged between 70 and 89 (N =70). It was

reported that approximately 94% of the patients could access their medication by opening bottles with screw caps. Success with blister packs was less than with the screw caps, ranging between 83 and 97%.⁹

Similar problems were reported via a postal survey of randomly selected members of the general public (N = 1,463) in order to determine their experiences with medicines packaging.¹⁰ With a 60% response rate and no indication of the respondent age distribution, generalisability was difficult to assess.

In the case of child – resistant containers and screw caps, a larger percentage of the group of respondents aged over sixty years reported difficulties extracting medication, than respondents from younger age bands. This trend was not reflected with blister packs as problems were reported by a greater percentage of younger people than the sixty years plus age group. The two problems that were most frequently reported with blister packs were difficulty in identifying whether they were full or empty and holding on to the contents after opening. The relative ease of blister packs may therefore be related to the size of the blisters although no research evidence is available to support this hypothesis.

The risk of blister packaging ingestion is further issue of concern which has been reported on numerous occasions, frequently resulting in damaging health consequences such as intestinal perforation and haemorrhage.^{11, 12}

A problem that is currently only applicable to items dispensed in the manufacturer's original packaging is the presence of tamper evident seals. These have been reported to cause inaccessibility problems for patients with mental, motor, and/or sensory disabilities.¹³

99 patients with arthritis of the hands were asked to assess twelve different containers manufactured by 10 pharmaceutical companies for ease of accessibility.¹⁴ Patients were given the containers in random order, asked to open them, extract the tablets, and close them. It was concluded that a successful container for arthritic hands is likely to have a 'sharply angulated or "wing" cap placed on a tall slim base that is also angulated. Flip off tops, tops with long threads requiring many turns, very small containers, and glass were regarded as unfavourable'.

2.2. Sight impairment

Sight impairment can affect a patient's ability to distinguish between their medicines, read container labels bearing directions and access medication from packaging. These effects result in a negative impact on adherence.¹⁵ Research has shown that a font size of 12-points or larger is necessary for patients with presbyopia to read.¹⁶ A method of facilitating patient identification of medications and the directions, proposed by Cramer, is colour coding of containers.¹⁶ It was proposed that use of a label of bright colour or marked with a letter (eg. 'A') would simplify identification. Further to this, if letters are used, a number could be added to the letter (eg. 'A2' for twice daily) to signify the number of daily doses. A list detailing the medicine names and full directions would need to be provided as reference for the patient.

2.3 Confusion / forgetfulness

The ability to understand directions and then have the cognitive function to remember them might be expected to be associated with unintentional non-adherence. This assumption is supported by the frequent reports of forgetfulness being cited as the reason for non-adherence.^{17,18} Several studies have demonstrated an association between cognitive impairment and adherence. In all cases, cognitive function was assessed via the Mini Mental State Examination (MMSE). The MMSE is an 11 question assessment of cognitive function scored out of 30. Traditionally the cut off for cognitive impairment is a score of 24 or less. Sensitivity at this cut off has been reported as 83% and specificity, 96%.¹⁹

Studies of 200 patients in Japan and 1979 in the Netherlands, using dosage unit count as the measure of adherence, found cognitive impairment to be a significant independent predictor of non-adherence.^{20, 21} A smaller study involving 178 patients considered cognitive function both as a continuous variable and dichotomised into impaired and non-impaired.¹⁷ No significant correlation was identified between cognitive impairment and adherence nor a significant difference between impaired and unimpaired groups in terms of adherence. Adherence was measured by dosage unit count where available, however, for 47% of the cognitively impaired patients, no dosage unit count result was available so self – reported adherence scores were used. The self – reported scores were calculated based on the respondents' response to the question: "How many pills do you usually miss a week?" Paucity of independent adherence assessment in this study may be the reason for the inability to identify a relationship between adherence and cognitive function.

It is difficult to make direct comparisons between the study results outlined above, due to wide inter study variation in average cognitive function of the sample populations. This may be a contributing factor to the differing associations reported between adherence and cognitive function. Considering the evidence available however, a positive association between cognitive function and adherence appears to exist but further research is necessary to confirm this.

2.4. Treatment regimen

The complexity of a treatment regimen has been found to adversely affect adherence. This includes both the number of different medications being taken concurrently and the dose frequency. A greater number of doses increases the probability of forgotten doses, as may a more complex regimen. Increasing the complexity may also reduce the likelihood of patients understanding their regimen.²²

A review of the adherence of forty elderly patients (age > 65 years) carried out by Kendrick *et al.* found that 65 % of the patients taking only one medicine had an acceptable level of adherence. Of those on four different types of medication, only 54% had acceptable adherence and when the number of medications was six, adherence fell a further 7%.²³ No comment was made by the author regarding what was considered acceptable adherence.

Hulka *et al.* showed a similar progressive decline in adherence with increasing number of medications from one to five. Any further increases in the number of different medications however, did not result in a significant change in adherence.²⁴

A retrospective cohort study that assessed adherence through patient questionnaire and computerised patient medication records found that the dosing frequency of medication was inversely correlated with adherence. The probability of a patient achieving 'high' adherence decreased by approximately 40% with an increase in one dose of medication per day.²⁵ Adherence was assessed as being high, medium or low using the self-reported Morisky scale.²⁶ Similar results were obtained in a study with more objective methodology, as a Medication Event Monitoring Systems container was used rather than patient self reporting.²⁷ An average of 79% of patients on once daily doses were considered to have adequate adherence, however, adherence was reduced to only 38% in the patients on a three times a day dose. Although total non-adherence was lower in the group on a once daily regimen compared to those taking medication three times a day, it was found that cases of addition were more common with once daily regimens. The medication used in

this study was oral antidiabetic agents where errors of addition may be just as detrimental as errors of omission.

The studies discussed above, comment on adherence with dose frequency, they do not however, address the issue of observing the recommended interval between doses. In the study conducted by Cramer *et al.* adherence with dose interval was monitored in addition to dose frequency.²⁸ Adherence with dose frequency was found to be greater than with dose interval. Of those patients on a twice daily regimen, the mean percentage (sd) of days on which medication was taken twice a day was 89 (7). However, only a mean percentage (sd) of 66 (24) of the doses were taken within the recommended 9-15 hour time interval. As with similar studies recording the effect of dose frequency on adherence, adherence decreased with increased dose frequency. There was also a decrease in interval adherence with increased dose frequency. For example, with a three times a day regimen, adherence with dose frequency was $80 \pm 18\%$ of days. The percentage of these doses that were taken within the correct interval of 6-10 hours was however a mean percentage (sd) of 40 (19). These values were further reduced with subsequent increases in dose frequency and hence decreases in dose interval window.

3. Intentional non-adherence

Reports of the incidence of intentional non-adherence range from 16.8%²⁹ to 35%.³⁰ Investigation into the causality of intentional non-adherence is however limited. Factors believed to be associated include the nature and duration of the drug treatment, quality of patient – prescriber interaction and psychological factors relating to the patient's personal beliefs.^{30 - 41} Whilst non-adherence is generally associated with underutilisation, overutilisation of certain medicines is also problematic^{42, 29, 43}

Interventions to address intentional non – adherence include the promotion of a concordant approach to prescribing in order to identify the treatment option most acceptable to the patient.

4. Interventions to facilitate adherence

Due to the wide variety of factors believed to contribute to non - adherence, the nature of interventions to improve adherence differ considerably. These range from educational to behavioural strategies and include various combinations of the two. Educational strategies can be delivered via several media including written information, audio-visual tapes or oral counselling. Behavioural strategies are interventions that facilitate an individual's ability to physically take their medication as recommended. Such strategies generally include Monitored Dosage Systems (MDS) (a type of MCA), administration and memory aids.

4.1 Educational strategies

Educational strategies have had varying degrees of success; Sackett *et al.*, randomised a group of patients on antihypertensive therapy to receive an educational programme.⁴⁴ It was designed to provide the patients with information on the effects that hypertension has on target organs, health, and life expectancy. They also provided information regarding the benefits of antihypertensives, the importance of adherence and 'tips' for remembering to take medication. They did not however, specify the nature of advice given to aid remembering to take medication. The information was provided both in the form of an audio - tape and booklet. The outcome of the study was that there was no significant improvement in adherence in the intervention group compared with the control. The intervention group did however, have significantly greater knowledge of hypertension and its management than the control group, suggesting that the educational programme was successful in achieving its educational aims. Interestingly however, an improvement in knowledge alone was not related to improved patient adherence.

Brus *et al.* investigated the effects of patient education on adherence with treatment regimens in recent onset active rheumatoid arthritis by randomly assigning patients to an intervention group to follow an educational programme or a control group.⁴⁵ Adherence was assessed via dosage unit counts and found to be high in both the intervention and control group with no significant difference between them.

An improvement in adherence due to education has been achieved by MacDonald *et al.*⁴⁶ who randomised 165 elderly patients to either receive counselling on their medication on hospital discharge or receive no intervention. Counselling patients were found to make less than one third of the errors made by uncounselled patients.

Despite the successful intervention made by MacDonald *et al.*, evidence for the effectiveness of purely educational interventions on adherence is limited. Smith *et al.* measured adherence in patients post discharge and found that 92% of the patients visited had over 95% adherence despite most having no understanding of the purpose of their medication.⁴⁷ These findings were supported by a review of research on adherence carried out by Pendleton that found only two thirds of the studies reviewed suggested an association between non-adherence and lack of medication knowledge.⁴⁸

Educational strategies have demonstrated varying levels of success in producing an improvement in adherence this may be partly attributable to the fact that their success is limited by the cognitive ability, visual acuity and manual dexterity of the patient. Also, educational strategies have traditionally focussed on unintentional non-adherence; helping patients to understand how to take their medication as directed. A further limitation of such strategies may therefore be that they do not directly address intentional non-adherence, that is, they are not tailored to individual needs.

4.2 Behavioural Strategies

Behavioural strategies are those which have been developed to help remind patients to take their medication. Cramer proposed three types of 'cue' that may be used (Table 1).

Table 1. Cues to facilitate adherence

Cue	Description
Clock time	Ask patient if they are usually aware of the time of day ie. do they consult a watch or clock regularly? If the answer is yes, arrange a twice daily dose to be taken at specific times of the day (eg. 7 am & 7 pm)
Meal time	Ask the patient if they eat meals at a regular time of the day. If the answer is yes, arrange medication to be taken at meal times
Daily ritual	Ask the patient about typical daily routines eg. tooth brushing, shaving, hair combing or walking the dog, picking up a newspaper. Link these to taking medication.

Adapted from: 'Enhancing patient compliance in the elderly. Role of packaging aids and monitoring.' *Drugs & Aging*. 1998;12(1):7-15

A small study carried out on thirteen open angle glaucoma patients, prescribed pilocarpine eye drops to be used four times a day, showed that adherence significantly improved with the use of a medication alarm device. Each patient acted as their own control as their adherence was measured over 30 days without the aid of the device and then for a further 30 days with the device. With the use of the reminder device, an average of 2.8g ($P = <0.0001$) more pilocarpine was administered over the 30 days than without the device.⁴⁹

The use of medication reminder charts is another intervention that has been found to be successful in improving adherence, as investigated by Raynor *et al.*⁵⁰ On hospital discharge, 197 patients were randomised to either receive counselling, a medication reminder chart with or without explanation. Patients receiving the reminder chart had significantly better adherence than those that did not. Furthermore, those that received an explanation of the chart had a higher mean adherence value than those that received the chart without explanation. As with educational strategies, memory aid success is limited by the cognitive ability, visual acuity and manual dexterity of the patient.

4.3 Summary

Winged caps have proved to be the easiest closure to manipulate and child resistant closures the most difficult. Reports related to blister packs are more varied and the ease of manipulation may be related to the size of the blister pack although evidence to support this hypothesis is unavailable. Inability to read the directions provided on pharmacy dispensed labels can be overcome by the provision of clearly labelled containers using colour coding or letter / number codes.

Educational interventions have improved patient understanding of medication regimens and possibly the importance of taking as directed. Cues and reminder charts have also been successful in prompting patients to take their medication. Educational strategy and memory aid success may however, be limited by impaired mental and / or physical function.

5. Multi compartment Compliance Aids (MCAs)

MCAs are usually a variation on the design of a box or a blister pack, divided into days of the week with several compartments per day to allow for the different timing of doses such as breakfast, lunch, dinner and bedtime. The proposed rationale for such devices Ref Nunney 51, Rivers 52, is presented in table 2.

Table 2 Potential benefits of MCAs

Potential benefit	Comments
Provide medicine storage which is easily accessible to the patient	The closures on many of the devices are designed to be easily manipulated by patients with impaired manual dexterity and / or visual acuity.
Reduce the complexity of adhering to a regimen	Medicines are pre-organized into individual compartments so the patient does not need to select doses from individual packaging
Minimise dose amount and timing errors	The dose to be taken and timing is pre-set by the organization of the medicines in the MCA
Act as a memory aid	Patients can identify whether or not doses have been taken

5.1 Evidence for beneficial effects of MCAs

Although the factors listed above seem intuitive, the evidence supporting the claims is sparse.^{52, 53} Randomized trials have been conducted; firstly comparing the effect on adherence of provision of a MCA (N = 184), secondly a comparison between the MCA and blister packs (N = 297). The outcome was that no significant difference in adherence was identified between patients that received no adherence aid, a MCA and blister packs.⁵⁴ The cohort that received the MCA had the responsibility of first filling the device from supplies provided in individual pharmacy dispensed bottles. The sample population was recruited via newspaper advertisement, resulting in a mean (sd) age of 58 (14), 46% with no disease history and over 43% with university or postgraduate education. The population in which the MCA was tested was not therefore representative of the population in which it is most likely to be used. The results of this study cannot therefore be generalizeable to a population with cognitive and / or physical impairment.

The packaging of medicines by manufacturers is increasingly in the form of ‘calendar packs’. These packs are similar in concept to MCAs as the days of the week are clearly marked and patients are able to see whether or not they have taken a dose. The results of studies relating to calendar packs may therefore be generalizeable to MCAs. A prospective, controlled, crossover study involving 22 older patients from an older persons clinic found calendar blister packs to significantly enhance adherence. Half of the patients received their medication from a commercially prepared calendar mealtime blister-pak; the remaining, received their medication from standard pharmacy dispensed bottles. At the end of three months the two groups were crossed over; adherence was assessed monthly via dosage unit count.⁵⁵

Potential problems associated with MCA’s^{51, 52} are presented in table 3 and the evidence available supporting such concerns is outlined below (section 5.2)

Table 3 Potential problems associated with MCAs

Potential problem	Comments
Error risk from secondary dispensing	
MCAs are not designed to address intentional non-adherence	May reduce patient autonomy by making it difficult for them to identify which medication they would like to omit but will not force a patient to take medication if they do not wish.
Only suitable for solid dosage forms that are to be swallowed whole	Dispersible, buccal or sublingual dosage forms cannot be included in MCAs, as such instructions cannot be applied to only one type of medication contained in the MCA. Also unsuitable for hygroscopic or photosensitive medication and medication prescribed to the patient on a “when required” basis as it may result in the patient unnecessarily taking it regularly. MCAs therefore, have the potential to create more confusion if some items are stored in the MCA and others in their original containers.
Long term stability unknown	
Risk of packaging ingestion with blister pack MCAs and certain monitored dosage systems	Section 2.1 discusses packaging ingestion.
Hygiene problems are associated with re-usable MCAs	Can become contaminated with bacteria and the powder of previously stored medicines.
Many do not have child resistant closures	It is professionally accepted that all dispensed medicines should be supplied in containers with child resistant closures unless otherwise requested by the patient.
Doses can become ‘mixed up’ if the MCA is dropped	When some MCAs are dropped, dosage units can move between compartments or fall out of the device.
Transportability	Patient acceptability in terms of the size of a MCA and hence ease of transport.

5.2 Evidence for potential problems associated with MCAs

Levings *et al.* conducted a study to identify problems arising with the use of MCAs.⁵⁶ Data regarding incidences associated with MCAs were obtained from forms completed in both the hospital and community setting for the Australian Incident Monitoring Study. Using a computer based search of the first 12,000 incidents reported, 52 were identified as involving an adherence device. The most common problem was that the system had been filled incorrectly, with nurses being responsible for over 80% of these filling errors; the remaining errors were made by pharmacists, doctors, the patient or carers. The second most common problem was that the patient made an error with a correctly filled MCA – dose omission, addition, or wrong medication. No indication was given as to how these errors were made.

It is accepted that MCAs are unsuitable for addressing intentional non-adherence as it reduces patient autonomy.⁵⁷ A far greater risk associated with MCA provision to address intentional non-adherence is that the patient will omit all medicines in a dosage compartment as they are unable to identify the medicine that they wish not to take.⁵⁸

There is little available data regarding the degradation of medicines once dispensed into MCAs. Walker surveyed pharmaceutical manufacturers regarding the stability of their products in daily dose reminders. These devices are not airtight nor are they resistant to light, however, manufacturers did not anticipate any degradation problems based on the assumption that the medicines would only be removed from their original packaging and stored in the device for approximately seven days and the filled device stored at an ambient temperature, protected from moisture and sunlight.⁵⁹ No studies have been identified which explore the impact on adherence of providing some medicines in a MCA and others in original or pharmacy dispensed packaging.

There is no evidence for the risk of packaging ingestion associated with MCAs however, it must also be reinforced to those dispensing into MCAs that cutting up blister strips and including the whole item into a MCA is unacceptable practice. This method has been used in order to include items into a MCA that should not be removed from the blister in advance of administration. This practice has resulted in patients ingesting the medicine together with the encasing packaging.⁶⁰

5.3 The role of the pharmacist in MCA provision

As the primary supplier of filled MCAs, pharmacists have been frequently used as the assessing health care professional (HCP) for MCA provision. This has generally been incorporated into

domiciliary services involving medication reviews, with one option to facilitate adherence being MCA provision.⁶¹ The value of incorporating medication review into adherence assessment is firstly, that rationalization of prescribing is a means of facilitating adherence; adherence is related to the number of prescribed drugs and complexity of regimen.^{23, 25, 28} Secondly, if adherence is to be improved, it is essential that the patient is in receipt of the appropriate therapy.

Considering the problems associated with MCAs (discussed previously), it is essential that they are supplied only to those patients that will benefit. Research has however, demonstrated that despite structured guidance regarding MCA provision, pharmacists have provided MCAs inappropriately. This has resulted in reduced patient autonomy, patient inability to access medication from the device and thus poorer therapeutic management.^{57, 58}

The high incidence of MCA provision by community pharmacists may be partly due to the direct association between MCA provision and remuneration for filling the device. A pilot study involving community pharmacists conducting domiciliary visits resulted in 90% of patients being provided with a MCA.⁶² The main service developed from this pilot provided similar pharmacist training however, the domiciliary visit was not conducted by the supplying pharmacist. The resulting proportion of patients that were provided a MCA was dramatically reduced to 10%.⁶³

It is therefore necessary to ensure that the assessment tool used to determine whether a patient will benefit from a device and identify the type of device, is rigorous and not open to interpretation by the pharmacist, introducing the potential for inappropriate device provision.

6. Recommendations

1. Design of a rigorous assessment tool via piloting, for use by community pharmacists to determine whether a MCA will benefit the patient.
 - Distinguish intentional non-adherence from unintentional
 - Consider methods of facilitating adherence
 - Reminder chart
 - Cues
 - Bottles with winged caps
 - Larger font / coloured / coded labels
 - Rationalize therapy
 - MCA
 - If a MCA is required, select the most appropriate aid for the individual patient

2. Generate a list of suitable MCAs based on:
 - patient accessibility
 - function as medication storage container
 - convenience of transport
 - child safety
 - 'drop ability'

7. References

- 1 Sackett, D.L, Snow, J.C. The magnitude of compliance and non-compliance. In: Haynes RB et al. (Eds) Compliance in health care. Baltimore, John Hopkins University press 1979; Nov-22
- 2 Levy, M, Lipshitz, M, Eliakim, M. Hospital admissions due to adverse drug reactions. The American Journal of the medical sciences 1979; 277(1):49-55
- 3 Hutcheon, A.W, Lawson, D.H, Jick, H. Hospital admissions due to adverse drug reactions. Journal of clinical pharmacy 1978; 3:219-24
- 4 Miller, R.R. Hospital admissions due to adverse drug reactions. Archives of Internal Medicine 1974; 134:219-23
- 5 Col, N, Fanale, J.E, Kronholm, P. The role of medication non-compliance and adverse drug reactions in hospitalisations of the elderly. Arch Intern Med. 1990; 150:841-5
- 6 Wasserefallen, J.B, Livio, F, Buclin, T, Tillet, L, Yersin, B, Biollaz, J. Rate, type, and cost of adverse drug reactions in emergency department admissions European Journal of Internal Medicine 2001; 12(5):442-447
- 7 Anon. Continuing education The Pharmaceutical Journal 2000; 264:476-479
- 8 Anon. Continuing education The Pharmaceutical Journal 2000; 264:57-68
- 9 Cubbin, S, Sexton, J, Bresnan, G, Kennedy, J.. Can elderly people manage their blister packs? United Kingdom Clinical Pharmacy Association: Proceedings of Residential Symposium 1993; 85-6
- 10 Rees, J.A, Forbes, A.J, Ross, A.J. Difficulties in the use of medicine packaging The International Journal of Pharmacy Practice 1992; 160-3
- 11 Fulford, S, Tooley, A.H. Intestinal perforation after ingestion of a blister-wrapped tablet Lancet 1996; 347(8994):128-9
- 12 Chan FK, Sung JJ, Tam PY, Kwong KH, Lau JW.. "Blister pack"-induced gastrointestinal hemorrhage American Journal of Gastroenterology 1997; 92(1):172-3
- 13 Sherman FT. Tamper-resistant packaging: is it elder-resistant, too? Journal of the American Geriatric Society 1985; 33(2):136-41
- 14 Le Gallez P, Bird HA, Wright V, Bennett AP.. Comparison of 12 different containers for dispensing anti-inflammatory drugs. Br Med J (Clin Res Ed). 1984; 288(6418):699-701
- 15 Nikolaus T, Kruse W, Bach M, Specht-Leible N, Oster P, Schlierf G. Elderly patients' problems with medication. An in-hospital and follow-up study European Journal of Clinical Pharmacology 1996; 49(4):255-9
- 16 Cramer, J.A. Enhancing patient compliance in the elderly. Role of packaging aids and monitoring. Drugs & Aging 1998; 12(1):7-15
- 17 Spiers, M.V, Kutzik, D.M. Self - reported memory of medication use by the elderly American Journal of Health - System Pharmacists 1995; 52:985-90
- 18 Conn, V., Taylor, S., Miller, R.. Cognitive impairment and medication adherence Journal of Gerontological nursing 1994; 20:41-7
- 19 Aevansson, O, Skoog, I. A Longitudinal Population Study of the Mini-Mental State Examination in the Very Old: Relation to Dementia and Education Dementia and Geriatric Cognitive Disorders 2000; 11(3):166-175
- 20 Okuno, J, Janagi, H, Tomura, S. Is cognitive impairment a risk factor for poor compliance among Japanese elderly in the community?
- 21 Salas, M, van der Linden, P, Hofman, A, Breteler, M, Stricker, B. Impaired cognitive function and compliance with antihypertensive drugs in elderly: the Rotterdam Study. Clinical Pharmacology and Therapeutics. 2001; 561-6

- 22 Ley, P. Giving information to patients. In: Eiser, J.R. ed. Social psychology and behavioural medicine. New York:John Wiley. 1982;
- 23 Kendrick,R, Bayne, J.R. Compliance with prescribed medication by elderly patients Canadian Medical Association Journal 1982; 127(10):961-2
- 24 Hulka, B.S. Medication Use and misuse: Physician-patient discrepancies. Journal of Chronic Disease 1975; 28:7-21
- 25 Sung, J. C.Y, Nichol,M.B, Venturini, F, Bailey, K.L, Cody, M.. Factors affecting patient compliance with antihyperlipidemic medications in an HMO population. The American Journal of Managed Care 1998; 4(10):1421-30
- 26 Morisky, D.E, Green, L.W, Levine, D.M. Concurrent and predictive validity of a self-reported measure of medication adherence. Medical Care 1986; 24(1):67-74
- 27 Paes, A.H.P, Bakker, A, Soe-Agnie, C.J. Impact of dosage frequency on patient compliance. Diabetes Care 1997; 20(10):1512-1517
- 28 Cramer, J, Vachon, L, Desforges, C, Sussman, N.M. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial Epilepsia 1995; 36(11):1111-7
- 29 Hoffmann, N.G, Olofsson, O, Salen, B, Wickstrom, L. Prevalence of abuse and dependency in chronic pain patients International journal of the Addictions 1995; 30(8):919-27
- 30 Bjorn, I, Backstrom, T. Drug related negative side-effects is a common reason for poor compliance in hormone replacement therapy Maturitas 1999; 32:77-86
- 31 Rashid, A.. Do patients cash prescriptions British medical journal 1982; 284:24-6
- 32 Jones,I, Britten, N.. Why do some patients not cash their prescriptions? British Journal of General Practice 1998; 48:903-5
- 33 Waters, W.H.R, Gould, N.V, Lunn, J.E. Undispensed prescriptions in a mining general practice British medical journal 1976; 1:1062-3
- 34 McElnay, J.C, McCallion, C.R, Al-Deagi, F. Self-reported medication non-compliance in the elderly European Journal of Clinical Pharmacology 1997; 53:171-8
- 35 Kiortsis, D.N, Giral, P, Bruckert, E, Turpin, G. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients Journal of Clinical Pharmacy and Therapeutics 2000; 25:445-51
- 36 Charney, E. Patient-doctor communication. Implications for the clinician. Paediatric Clinics of North America 1972; 19(2):263-79
- 37 Beardon, P.H.G, McGilchrist, M.M, Mckendrick, A.D, McDevitt, D.G., MacDonald, T.M. Primary non-compliance with prescribed medication in primary care The British Medical Journal 1993; 307:846-8
- 38 Gopinath, B, Radhakrishnan, K, Sankara Sarma, P, Jayachandran, D, Alexander, A. A questionnaire survey about doctor-patient communication, compliance and locus of control among South Indian people with epilepsy Epilepsy Research 2000; 39:73-82
- 39 Ried, D.L, Oleen, M. A, Martison, O.B. Explaining intention to comply with antihypertensive regimens. Journal of Social & administrative Pharmacy 1985; 3:42-52
- 40 Donovan, J.L, Blake, D.R. Patient non - compliance: Deviance or reasoned decision - making. Social Science Medicine 1992; 34(5):507-13
- 41 Fallsberg, M.. Reflections on medicines and medication: a qualitative analysis among people on long - term drug regimens. PhD Thesis 1991; Linkoping, Sweden: Linkoping University
- 42 Kouyanou, K, Pither, C.E, Wessley, S. Medication misuse, abuse and dependence in chronic pain patients Research 1997; 43(5):497-504

- 43 McBride, A.J, Meredith-Smith, P. Compound opioid-paracetamol analgesics: misuse and dependence *British Journal of Clinical Practice* 1995; 49(5):268-9
- 44 Sackett, D.L, Haynes, B.R, Gibson, E.S, Hackett, B.C, Taylor, D.W, Roberts, R.C, Johnson, A.L. Randomised clinical trial of strategies for improving medication compliance in primary hypertension *The Lancet* 1975; 1:1205-7
- 45 Brus, H.L, van de Laar, M.A, Taal, E, Rasker, J.J, Wiegman, O. Effects of patient education on compliance with basic treatment regimens and health in recent onset active rheumatoid arthritis. *Annals of the Rheumatic Diseases*. 1998; 57(3):146-51
- 46 MacDonald, E.T, MacDonald, J.B, Phoenix, M. Improving drug compliance after hospital discharge *British medical journal* 1977; 2(6087):618-21
- 47 Smith, P, Andrews, J. Drug compliance not so bad, knowledge not so good: the elderly after hospital discharge. *Age and Ageing*. 1983; 0.7333333333333333
- 48 Pendleton, D. Knowledge and compliance: not linked after all? *The Pharmaceutical Journal* 1992; 196
- 49 Laster, S.F, Martin, J.L, Fleming, J.B. The effect of a medication alarm device on patient compliance with topical pilocarpine *Journal of the American Optometric Association* 1996; 67(11):654-8
- 50 Raynor, D.K, Booth, T.G, Blenkinsopp, A.. Effects of computer generated reminder charts on patients' compliance with drug regimens *British medical journal* 1993; 306:1158-60
- 51 Nunney, J, Raynor, D.K. How are multi - compartment compliance aids used in primary care? *The Pharmaceutical Journal* 2001; 267:784-9
- 52 Rivers, P.H. Compliance aids - do they work? *Drugs & Aging* 1992; 2(2):103-11
- 53 Insull, W. The problem of compliance to cholesterol altering therapy *Journal of internal medicine* 1997; 241:317-25
- 54 Huang HY, Maguire MG, Miller ER 3rd, Appel LJ. Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplementation trials. *American Journal of Epidemiology* 2000; 152(8):780-7
- 55 Hurd PD, Butkovich SL. Compliance problems and the older patient: assessing functional limitations *Drug Intell Clin Pharm* 1986; 20(3):228-31
- 56 Levings, B, Szep, S, Helps, S.C. Towards the safer use of dosettes *Journal of quality in clinical practice* 1999; 19:69-72
- 57 Nunney, J, Raymor, D.K. Mind the gap: how compliance aids increase the distance between patients and their medicines. *The International Journal of Pharmacy Practice* 2001; 9(suppl):R46
- 58 Bhattacharya, D. Pharmacist domiciliary visiting: derivation of a viable service model PhD Thesis 2003; University of Bradford
- 59 Walker, R. Stability of medicinal products in compliance devices. *Pharmaceutical Journal*. 1992; 25:124-6
- 60 Sexton, J, Gokani, R. Pharmaceutical packaging and the elderly *The Pharmaceutical Journal* 1997; 259:697-700
- 61 Bhattacharya, D, Wright, D.J, Purvis, J.R. Pharmacist domiciliary visiting: review of English services *The Pharmaceutical Journal* 2003; 271:(suppl):R8
- 62 Hinde, M.. Pharmacy Outreach project - second interim report. *The Hinde Consultancy* 1998;
- 63 Holland,R, Lenaghan, E, Harvey, I, Smith, R, Shepstone, L. Does home-based medication review keep older people out of hospital? Accepted for publication