

Appendix 6. Detailed description of the results based on intervention type

Reminders

8 studies used reminder interventions (SMS, alarm device or IVR-calls) and two of these studies showed a statistically significant improvement in adherence. In Lester 2010(60) and Mbuagbaw 2012(61) cited by Mathes, Antione et al. 2014(59), SMS interventions were used to improve adherence. Lester 2010 showed a statistically significant improvement in adherence, with an observation period that was twice as long as in Mbuagbaw 2012. In addition, the intervention was more far-reaching since the patients received a call if they reported a problem or did not respond to the SMS within two days. There were four different adherence results in Mbuagbaw 2012 and only one of them showed a statistically significant improved adherence. It was not reported how many patients that reached improvement. Because the other three results did not show improvement, the whole study was considered to have a negative result by the author of this report.

As described in Ngwatu, Nsengiyumva et al. 2018(63), Bediang 2014(64) and Mohammed 2016(66) daily automated SMS reminders to improve adherence among patients with tuberculosis, but the adherence measures were not reported. In the same systematic review, Liu 2015(65) compared two-way SMS, MM (medication monitor) and combination of two-way SMS and MM, to DOT without reminders. The two-way SMS intervention reported the highest percentage of non-adherence (30 %), that was identical to the control group. The results from the intervention with MM and SMS/MM were statistically significant but not for the SMS group. The results indicated that the medication monitor had a stronger influence on improving adherence than two-way SMS.

As cited in Nieuwlaat, Wilczynski et al. 2014(13), Sherrard 2009(78) used IVR-calls in both groups, with less calls in the control group. Compliance in the intervention group was significantly higher than in the control group. Increased call frequency might not be responsible for that result alone, since the intervention group also were called by a nurse that offered education and counselling. In the same systematic review, Chung 2011(68) used alarm device intervention that showed no improvements in adherence. In Normansell, Kew et al. 2017(82) the interactive voice call results on adherence in NCT00414817(84-86) were not reported.

SMS, IVR-calls and alarm devices are assumed to demand less economic and humanistic resources by the intervention provider compared to the other interventions presented in this report. These practical strategies will be more suitable for unintended non-adherers, since they get a signal that reminds them to take their medication(16). On the other hand, the patients can ignore the reminder, making this intervention type not suitable for enhancing adherence among intentional non-adherers.

The type of non-adherence was not reported, so it's not certain if the intervention targeted a population that could benefit from the interventions. In addition, when the reminder interventions were compared to DOT, which is a strong intervention itself, it's difficult to evaluate the value of reminder interventions to usual care which often is no intervention. The results are in accordance with previous results showing some positive but mixed effects on adherence using practical intervention strategies(106).

Simplifying dosing

3 studies had a simplified dose regimen as intervention, only one of them improved adherence. As described in Nieuwlaat, Wilczynski et al. 2014(13), there was no statistically significant effect on adherence to HIV/AIDS or heart failure medication in Dejesus 2009(69) and Udelson 2009(79), respectively. In Price 2010(87), cited in Normansell, Kew et al. 2017(82), there was a statistically significant improvement of adherence to inhaled medicine for patients with asthma when the dosing frequency was halved. These results are not fully in accordance with previous results that showed a positive effect on adherence when the dosage regimen was simplified(106). It's unclear if the patients in the three studies were screened for non-adherence to multiple dosing before the study started. This intervention would have been suitable for patients that forget to take their medication or patients that feel that their medication-intake is in conflict with their daily routine(16).

DOT

4 studies reported DOT (Directly Observed Treatment) as intervention, and one of them showed improved adherence. In Sarna 2008(62), cited in Mathes, Antoine et al 2014(59), the medication intake was observed by a nurse. Adherence was statistically improved but only during the intervention period. In Bediang 2014(64), cited in Ngwatu, Nsengiyumva et al. 2018(63) DOT was used both in the intervention group and in the control group, but the intervention group received SMS reminders in addition. Adherence results were not reported. In the same systematic review, Mohammed 2016(66) compared SMS reminders to DOT, but adherence measures were missing. In contrast, DOT showed a worse non-adherence when compared to two-way SMS and medication monitor in Liu 2015(65). This was in accordance to what was found in the overview of the systematic reviews, where DOT interventions had some negative and ineffective impact on adherence and clinical outcomes, in addition to being an ineffective intervention(106). In the systematic review Bediang 2014(64), Mohammed 2016(66) and Liu 2015(65) were included, the authors suggested

using digital technologies instead of DOT, since DOT can be challenging to implement and requires intensive resources(63).

DOT is a powerful intervention by means that it affects the patients' daily routine, especially in the cases where it involves a clinic visit for observation of medication intake. The intervention might also lead to a feeling of loss of empowerment among the patients and can be time consuming and demanding on health care resources. As one of the studies showed, the effect of the intervention ceased in the follow-up period. And the other study showed that DOT lead to worse non-adherence compared to other more resource friendly interventions. The four studies took place in Kenya, Cameroon, Pakistan and China. The intervention might not be suitable for high-cost countries.

Education

11 studies reported education as intervention, whereas 8 of the reported a positive effect on adherence.

As described in Al-aqeel, Gershuni et al. 2017(56), one-on-one education provided by an epilepsy nurse resulted in a tiny statistically significant improvement of adherence in the intervention group in Dash 2015(57), and a tiny improvement in the control group that was not statistically significant. In Levy 2000(72), cited in Nieuwlaat, Wilczynski et al 2014(13), nurse provided education led to statistically significant improvement for severe attacks but not for mild attacks of acute asthma.

As described in Nieuwlaat, Wilczynski et al. 2014(13) education was performed by a pharmacist in Holland 2007(71), Murray 2007(73), Nazareth 2001(74) and Sadik 2005(77). Holland 2007 and Nazareth 2001 had similar content in their interventions for the patients that were discharged but the intervention in Nazareth 2001 was more complex. In both studies the pharmacists made patient home visits. Either two of the studies had a statistically significant effect on adherence. In a more recent systematic review examining the effect on adherence interventions, it was found that face-to-face interventions delivered directly to patient by pharmacists was the most effective medication adherence interventions, but the interventions delivered at patients' homes were less effective compared to interventions delivered at pharmacies and clinics(107).

Sadik 2005(77) showed a statistically significant improvement of adherence for the patients that received education, and some of the patients were also given a simplified dosage regimen. In Murray 2007(73) the pharmacist intervention showed a statistically significant positive effect on adherence based on MEMS and pharmacy refills, but the patients reported no effect on adherence through self-

report. In Mehuys 2008(83), cited in Normansell, Kew et al 2017(82) the patients' adherence to asthma inhalers was a statistically significant increase in the intervention group.

Jarab 2012(97), Khmour 2009(98), Wei 2013(100, 101) and Weinberger 2002(102), all described in Zhong, Ni et al. 2014(96), showed adherence improvement in the intervention groups that received pharmacist education, however Weinberger 2002 did not have a statistically significant result. The overview of systematic reviews reported that education as single intervention appeared ineffective to improve adherence and clinical outcomes but could improve knowledge and thereby the patients ability to make informed medicines choices(106). This can be useful for patients with intentional non-adherence, assuming that concordance methodology might be suitable for their needs. Further Ryan et al pointed out that education in combination with other interventions may improve adherence and clinical outcomes, but the results were mixed(106). This is in accordance to what was found in the studies that provided education, there were also other components of interventions in addition to education. In a review Jimmy and Jose stressed that clear medication related information was essential to improve adherence. Patients' needs to have key information about what, why, when, how and how long, and they should also be provided written information about their medications(18), as the patients first have to understand the instructions to successfully follow them(15).

Counselling

4 studies had counselling as intervention, 2 of them reported a statistically improved adherence. All the four studies Pyne 2011(76), Bond 2007(67), Wu 2006 (81) and Nieuwkerk 2012(75) were described in Nieuwlaat, Wilczynski et al. 2014(13).

In Pyne 2011(76) there was a team existing of a nurse, pharmacist and psychiatrist that had telephone counselling with the patients. The care teams' communication did not result in statistically significant improvement of adherence.

In Bond 2007(67), the consultation(s) with the pharmacist with focus on appropriateness of medication and compliance did not lead to any statistically significant improvement in adherence. In contrast, telephone counselling by a pharmacist every 2-4 month for 2 years lead to a statistically significant improvement in Wu 2006(81). In that study the patients' adherence was assessed prior to the start of the intervention period.

In Nieuwkerk 2012(13), a nurse counselled the patients about their increased cardiovascular risk and how to prevent the incidents. The patients' self-report revealed showed a statistically significant positive effect on adherence.

In the overview of systematic reviews there was some evidence that counselling was effective to improve adherence, but results were mixed. Interventions involving pharmacists showed improved adherence, but the evidence was insufficient to support more intensive care of patients by pharmacists (106). It must also be mentioned that the interventionist's profession can be of importance, especially when it comes to identifying, resolving and preventing drug-related problems. Due to Hepler and Strand there are three major functions that are involved in pharmaceutical care (38). This can support both the methods and the findings in Wu 2006. A recent systematic review reported that pharmacist delivered interventions were significantly more effective than interventions by other health care professionals(107). Since the effect sizes were not reported in the four studies, besides on mortality in Wu 2006(81), a discussion about effect was not possible.

Web based programs

2 studies used web-based programs as intervention and one of them showed improved adherence. Weeks, George et al. 2016(37), cited Magid 2013(90), where the patients in the intervention group used a web-based monitoring program for uploading the results of their home-measured blood pressure. There was little or no difference in adherence at 6 months, compared to control group. In Dilorio 2011(58) described in Al-aeel, Gershuni et al. 2017(56), the epilepsy patients that was signed up for a web-based program showed a slightly higher adherence than the control group after 12 weeks with a not statistically significant result.

Web-based program as in these two studies might empower the patients and develop a higher grade of patients' self-management, in addition to an improved insight to their conditions as they can be more involved in their own treatment. From the overview of systematic reviews there was reported that self-monitoring and self-management programs were generally effective in improving both adherence and clinical outcomes. Meanwhile, it was not suitable for everyone as not all the participants in studies followed the programs(106).

Prescribing pharmacists

4 studies had interventions with pharmacists that prescribed medication. One of the studies showed an improvement in adherence but it did not sustain throughout the observation period. All the four

studies Bruhn 2013(88), Hunt 2008(89), Magid 2013(90) and Margolis 2013(91) were described in Weeks et al. 2016 (37)

In Bruhn 2013(88) the pharmacist conducted a face-to-face review of the patients' medications in addition to prescribing, but it was unclear if there was any difference between the groups on adherence to pain relieving medications. In Hunt 2008(89) and Magid 2013(90), the pharmacist review and prescribing were more comprehensive, but there was probably little or no improvement in adherence to antihypertensive agents. In Margolis 2013(91) there was seen improved adherence in the intervention group simultaneously as the adherence in the control group decreased at the end of the most intense part of the intervention period (6 months). It was assumed that there was little or no difference at 12 and 18 months. This substantiates the allegations about adherence being a dynamic process that needs to be followed up continuously(14) as patients make a decision every day whether and how to take their medication(15). Also, patients can be non-adherent during different stages of their treatment(44), and most patients are non-adherent at some time in their treatment(25).

The interventions were delivered differently, from face-to-face, telephone and e-mail, and the interventions were complex. None of the studies revealed low adherence at the baseline, on the contrary, adherence was reported as high both in intervention groups and control groups. To reveal the true effect of the intervention, patients having insufficient adherence should have been screened prior to the study. In Bruhn, Hunt and Margolis the Morisky Medication Adherence Scale was used to measure adherence. This scale could also be used for identifying non-adherers prior to the study(108), as well as the Structured Medication Questionnaire used by clinical pharmacists in Sweden(109).

Another consideration of studies like this, is the participants in the study sample, and if they represent the general population. People who want to maintain a good health might have lower threshold for signing up for participating studies, and this can explain the high adherence rate at the baseline.

In the overview of systematic reviews, pharmacist interventions like medicines management, medicines reviews and pharmaceutical care serviced had a positive effect on adherence and clinical outcomes(106). Studies examining the effects of pharmacist prescribing and adherence can be of importance in the process of evaluating of pharmacist prescribing in Norway, as there is an ongoing discussion about implementing prescribing to the pharmacist role(110).

Physician interventions

4 studies examined the effect of providing physicians with their patients' adherence measures up-front appointments. None of the studies showed any statistically significant effect on adherence.

In Vergouwen 2005(80) cited in Nieuwlaat et al. 2014 (13), the general practitioners received information from patient self-reports before scheduled visits. Motivation interview was used to enhance the adherence. Zaugg, Korb-Savoldelli et al. 2018(92) described Pladevall 2015(93), Williams 2010(94) and Willis 2013 (95). In Pladevall 2015, the physicians had access to their intervention group patients' adherence and clinical test results. Similar intervention was reported in Williams 2010 and Willis 2013, accordingly having no change in adherence, and the result was not statistically significant.

It must be taken in to consideration that these studies were performed in the USA(92) and Canada(13), and therefore might not be generalisable for other parts of the world.

The studies did not report if the physicians received any adherence education. According to WHO, health care professionals need specific training and a system in their work that supports adherence management(14). The studies also did not report how the physicians worked to improve their patients' adherence. According to Jimmy and Jose, the health care providers need to identify the underlying causes of their patients' non-adherence to determine the appropriate intervention strategy(18). For instance, there is less point in increasing an individual's awareness of benefits of the medication if the problem of the patient is to remember to take the medication(22). Further, it is suggested that providers must create a treatment relationship that reflects a partnership with their patients, and support the discussion of therapeutic options, the negotiation of the regimen and clear discussion of adherence(14). The patient-practitioner relationship will determine the quality of the discussion. The information the provider gives, and how it is presented, must be evidence based and adapted to the situation and the patients' preferences and needs(9). Time duration of the visits can also be of importance, since short duration of medical visits may be a barrier to have the time for adherence-discussion(111). At the end, the patient's decision will be based on recommendations from the practitioner, and if the patient agrees that they are in the best interest for their health(15).

